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The effects of Mito-TEMPO, a mitochondria targeted antioxidant, on frozen human sperm parameters

Mitokondri hedefli bir antioksidan olan Mito-TEMPO'nun donmuş insan sperm parametreleri üzerindeki etkileri

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Abstract

Aim: The goal of this study is to find out if Mito-TEMPO, an antioxidant that targets mitochondria, can improve the quality of frozen human sperm.

Material-Method: Normospermic 25 human semen samples were frozen and stored in solutions including different concentrations (0, 5, 10 and 50 µM) of Mito-TEMPO. After thawing, they were evaluated in terms of sperm motility, viability, morphology, chromatin integrity and apoptosis.

Result: Sperm morphology was not found to change after cryopreservation. Viability was found to be significantly preserved in groups that were added Mito-TEMPO ($p<0.01$). When the motility of the sperms after they had been frozen was compared, the group that added 50 µM Mito-TEMPO had the most motile sperms. ($p<0.05$), even though there was no statistically significant difference between the groups that added 1 µM Mito-TEMPO and the groups that did not add Mito-TEMPO. In addition, chromatin decondensation and apoptosis rate decreased significantly in groups that were added Mito-TEMPO ($p<0.01$).

Conclusion: Mitochondria targeted antioxidant Mito-TEMPO improves sperm quality that decreases after thawing.

Keywords: Antioxidant, Cryopreservation, Mitochondria, Mito-TEMPO, Sperm.

Özet

Amaç: Bu çalışmanın amacı, mitokondri hedefli bir antioksidan olan Mito-TEMPO'nun donmuş insan sperm kalitesini iyileştirmedeki etkinliğini incelemektir.

Gereç ve Yöntem: Normospermik 25 insan semen örneği farklı konsantrasyonlarda (0, 5, 10 ve 50 µM) Mito-TEMPO içeren solüsyonlarda dondurularak saklandı. Çözme sonrası sperm motilitesi, viabilitesi, morfolojisi, kromatin bütünlüğü ve apoptozis bakımından değerlendirildi.

Bulgular: Kriyoprezervasyon sonrası sperm morfolojisi değişmedi. Viabilite Mito-TEMPO eklenen gruplarda önemli ölçüde korundu ($p<0.01$). Spermler kriyoprezervasyon sonrası motilite bakımından karşılaştırıldığında 1µM Mito-TEMPO eklenen grup ile Mito-TEMPO eklenmeyen grup arasında anlamlı bir farklılık gözlenmezken en fazla motil sperme rastlanan grup ise 50 µM Mito-TEMPO eklenen grup oldu ($p<0.05$). Ayrıca kromatin dekondensasyonu ve apoptozis oranı Mito-TEMPO eklenen gruplarda önemli ölçüde azaldı ($p<0.01$).

Sonuç: Mitokondri hedefli bir antioksidan olan Mito-TEMPO çözme sonrası azalan sperm kalitesini iyileştirir

Anahtar Kelimeler: Antioksidan, Kriyoprezervasyon, Mitokondri, Mito-TEMPO, Sperm.

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INTRODUCTION

Cryopreservation describes the storage of biological materials such as liquid nitrogen at cryogenic temperatures and using these when needed . Sperm freezing is an ideal solution to preserve fertility before surgical procedures as well as cytotoxic treatment such as chemotherapy and radiotherapy . Despite extensive advances in this area, Not all of the biological and biochemical parts of cryopreservation have been figured out . It is well known that at low temperatures, cell metabolism slows down, which protects germ cells, embryos, and tissues in the long run . But many things during the freezing process, like sudden changes in temperature, ice formation, and osmotic stress, have been thought to be the cause of low-quality sperm . In addition, studies have proven that cryopreservation of sperm leads to the induction of damage such as plasma membrane and mitochondrial dysfunction, DNA damage, loss of motility and viability . During the cryopreservation process, oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the production of antioxidants . Antioxidants in seminal plasma protect sperm cells from damage caused by oxidative stress. But taking out the seminal plasma, which has antioxidants, during cryopreservation lowers oxidative stress .

A large number of studies carried out recently showed that adding antioxidant during cryopreservation can neutralize ROS and improve sperm functions after freezing . However, there are few studies which show that oxidative stress is minimized by targeting ROS production sites in spermatozoa . In this regard, mitochondria, which are known as an important site of ROS production, have received great attention. Mitochondria are one of the main targets of ROS. Therefore, mitochondria targeting antioxidants have been proposed as new treatments in the last few years .

Mito-TEMPO is a compound made up of cations that like to stick to fat. It gets rid of ROS well because it has superoxide dismutase activity. It is a mix of tempo and triphenylphosphonium, which is a compound meant to get rid of superoxide in the mitochondria. It can build up about 500 times in the mitochondria and oxidizes iron ions to clean them out of the body. So, it stops the formation of hydroxyl radicals and the Fenton reaction in the oxidative chain reaction in the mitochondria. In some diseases, Mito-TEMPO has been shown to protect against damage caused by oxidation. Mito-TEMPO is known to be a good antioxidant, but it is clear that we don't know enough about how it protects sperm during cryopreservation .

The goal of this study is to find out how Mito-TEMPO, an antioxidant that works on mitochondria, affects human sperm parameters after they have been frozen.

MATERIAL and METHODS

This experiment was done on waste sperm from men between the ages of 20 and 45 who had gone to the Bolu Abant İzzet Baysal University Faculty of Medicine for a spermiogram test. The people who took part in the study were asked to sign a consent form. The study was done with permission from the Bolu Abant İzzet Baysal University Faculty of Medicine Clinical Research Ethics Committee, which gave them the number 2019/103.

Chemicals

All the chemicals were bought from Sigma Aldrich.

Preparing the semen samples

Semen samples from 25 men who had not been sexually active for 3 days were kept on a heating surface at 35°C for 30 minutes to melt them. After that, they were looked at both with a big (macroscopic) and a small (microscopic) lens (concentration, motility, viability, morphology). WHO 2020 criteria meant that normal sperm samples were part of the study (Table 1).

Table 1 Cut-off reference values for normal semen characteristics as published in consecutive WHO manuals and values in this study

PARAMETERS	WHO 2020	Values in this study
Semen volume (ml)	≥ 1.4	2.88
Sperm concentration (10^6/ml)	≥ 16 (12-16)	73.17
Total motility (PR*+NP*,%)	≥ 40 (38-42)	58.1
Viability (%)	≥54	75.1
Sperm morphology (normal form, %)	≥4.0	11.76
pH	≥7.2	≥7.2
Peroxidase-positive leukocyte (10^6/ml)	<1.0	<1.0

*PR: Progressive, *NP: Non-progressive

Sperm Cryopreservation and Thawing

After putting each sample of normal sperm in a centrifuge at 1000 rpm for 10 minutes, they were homogenized by adding 1:1 sperm washing medium (FertiPro, Belgium, Lot: FP22FL06) on the pellet obtained. After this, each of the semen samples was divided into equal volumes of cryotubes. In the first group, 3% dimethyl sulfoxide (DMSO) was added slowly to the first group as cryoprotectant and it was considered as the control group. Different concentrations (5 µM-10 µM-50 µM) of Mito-TEMPO (CAYMAN, CAS Number:1569257-94-8, USA) were added with DMSO (Sigma-Aldrich, Cat No.41639, U.S.) to the other groups, respectively. After the groups were cooled for 10 minutes in nitrogen vapour, They were put in a tank with liquid nitrogen and frozen. After 72 hours, the samples were taken out of the tank of liquid nitrogen and thawed at 37 °C for 10 minutes. To get rid of the DMSO and Mito-TEMPO, they were spun at 1000 rpm for 10 minutes. After adding 1:1 sperm washing medium to the pellet to make

it homogeneous, it was left to sit for about 30 minutes. The samples were then examined by sperm parameters.

Evaluation of Sperm Motility, Viability and Morphology

After the samples were incubated, the makler counting chamber was used to measure how active they were (Sefi Medical Instruments). WHO 2020 criteria were used to do the mobility assessment. Sperm motility was measured in terms of whether progressive, non-progressive and immotile at all. Sperm concentration was also taken into account. Eosin-Y stain was used to test sperm viability and morphology. This method is a test based on the selective permeability of the cell membrane (11). 1/1 Eosin-Y solution and the sperm sample were mixed on a slide, 200 sperm cells in different areas were counted for viability and morphology. The cells which did not receive the eosin stain were evaluated as viable and pink cells were evaluated as non-living; morphology assessment was made according to WHO 2020 criteria and viability and morphology percentage were calculated for each sample.

Chromatin Condensation Evaluation

Samples of thawed sperm were used to make smears, which were then air-dried. For acidic aniline blue staining, group smears were fixed for 10 minutes with 3% glutaraldehyde (Merck, Cat No. 8206031000, Germany). After that, they were stained with acidic aniline blue for five minutes (Carlo Erba, Cat. No. 428582, France) (pH: 3,5). After that, the specimens were rinsed in phosphate buffer solution (Phosphate Buffered Saline, PBS, Thermo Fisher Scientific, UK, pH 7.2).

Aniline blue is a standard test for finding out if sperm DNA has chromatin condensation (12). Condensed sperm with histones that are high in lysine are stained dark where the nuclei are. Light is used to stain the arginine and cysteine in the sperm's protamine nucleus (13). Under a Nikon Eclipse 80i light photomicroscope, 200 sperm cells that had been stained with acidic aniline blue were looked at. The X100 lens was used to take pictures of them.

Apoptosis Assessment

Apoptosis was done by following the instructions on the TdT mediated dUTP Nick-End Labeling (TUNEL) kits (Millipore, USA). Sperm samples were put on poly-lysine-coated slides and dried at room temperature after being spun down and washed with PBS. In a staining process that followed the instructions from the manufacturer, the preparations were left at 37 °C for 60 minutes with a TUNEL mixture, and DNA fragments were marked. DAB was passed through chromogen and alcohol series after counter staining and coated with entellan. The Nikon Eclipse 80i light photomicroscope was used to count and study 200 sperm cells in each preparation. The X100 lens was used to take pictures of them.

Statistical Analysis

Statistical analyses of the study were performed with SPSS version 26.0 analysis program. Normality distribution of the groups was evaluated with Shapiro-Wilk Test. When it was found that all of the data were not normally distributed, the data were expressed as median±IQR. Differences of data between groups were evaluated with Kruskall-Wallis Test, which is a non-parametric test. Individual group differences were evaluated with post-hoc analysis Bonferroni Test. The level of significance was set at $p \leq 0,05$.

RESULTS

This study was done with sperms from people who asked for a semen analysis. According to WHO 2020 criteria, the study included samples from people with normal sperm. The effect on sperm parameters of adding different amounts of Mito-TEMPO to solutions used for cryopreservation was studied. When Mito-TEMPO was used instead of pre-cryopreservation, the percentage of cells with normal shape didn't change. It was found that the number of viable sperm cells was much lower after cryopreservation than before ($p<0.01$). When the groups' viability after cryopreservation was compared, the Mito-TEMPO group was found to have kept its viability much better than the other groups ($p<0.01$) (Figure 1).

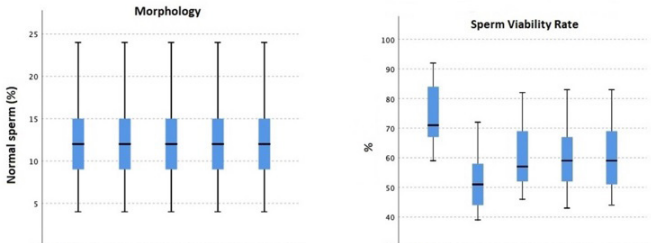

Figure 1. Pre-cryopreservation and post-cryopreservation morphology and viability values of the related groups.

When comparing the motility of all groups before and after cryopreservation, it was found that all groups had less motility after cryopreservation ($p<0.05$). When the groups were compared after cryopreservation, the highest motility loss was found in the group which was not added Mito-TEMPO ($p<0.05$). There was no significant difference between the group that got 1 µM Mito-TEMPO and the group that didn't get any, but the groups that got 10 µM and 50 µM Mito-TEMPO still moved around. The group to which 50 µM Mito-TEMPO was added had the most sperm that could move ($p<0.05$) (Figure 2).

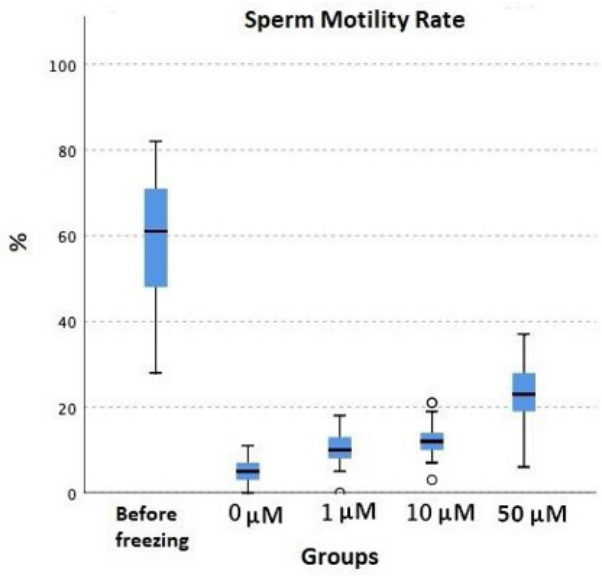

Figure 2. Pre-cryopreservation and post-cryopreservation motility values of the related groups.

When the groups were compared in terms of chromatin condensation, the rate of decondensed sperm was highest in the group that was not added Mito-TEMPO as a result of aniline blue staining ($p<0.01$) (Figure 3). When the group that was not added Mito-TEMPO and the groups that were added 1 µM and 10 µM Mito-TEMPO were compared, although fewer decondensed sperms were found in the group that was added 10 µM Mito-TEMPO, no statistical significance was found. The group closest to the chromatin condensation rate of sperm before cryopreservation was the group that was added 50 µM Mito-TEMPO ($p<0.05$) (Figure 4).

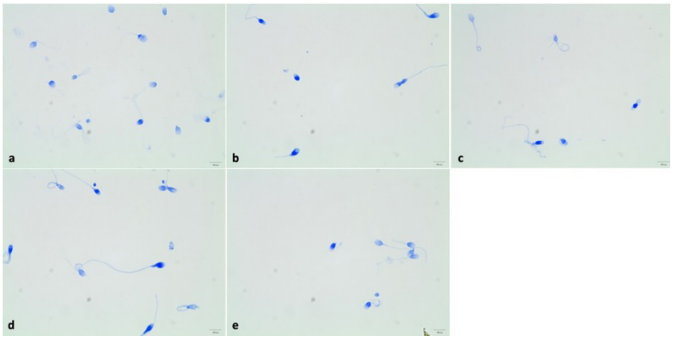

Figure 3. Pre-cryopreservation group (a), 0 µM Mito-TEMPO group (b), 1 µM Mito-TEMPO group (c), 10 µM Mito-TEMPO group (d), 50 µM Mito-TEMPO group, (d) 1000X, Scale bar: 10 µm. Condensed sperms are seen to be lightly stained with acidic aniline blue in pictures a, b, c, d and e; decondensed sperms are seen to be darkly stained with aniline blue in pictures a, b, c, d and e.

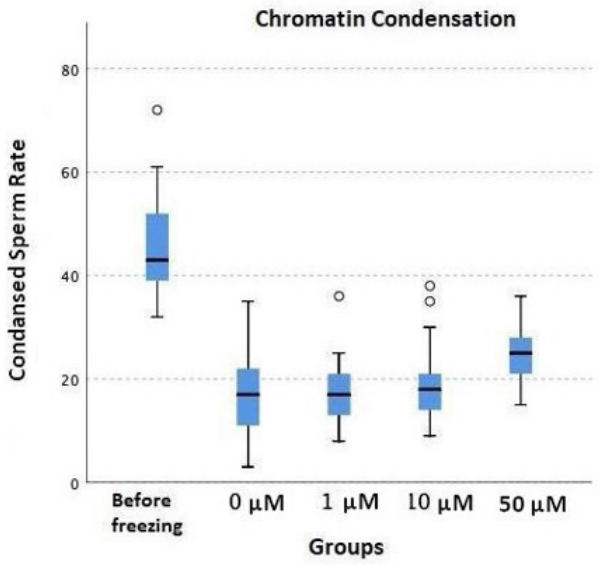

Figure 4. Pre-cryopreservation and post-cryopreservation condensed sperm values of the related groups.

When the sperm cells were compared in terms of apoptosis as a result of TUNEL staining (Figure 5), the apoptosis rate in Mito-TEMPO added groups (1µM -10µM -50µM) was statistically significantly lower than the group that was not added Mito-TEMPO ($p<0.05$) (Figure 6).

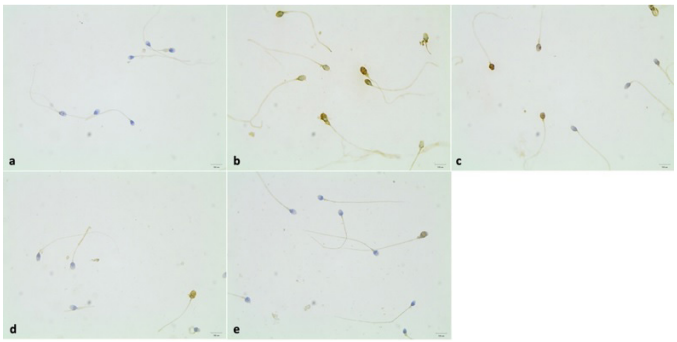

Figure 5. Pre-cryopreservation group (a), 0 µM Mito-TEMPO group (b), 1 µM Mito-TEMPO group (c), 10 µM Mito-TEMPO group (d), 50 µM Mito-TEMPO group, (d) 1000X, Scale bar: 10 µm. Apoptotic sperms are seen to be brown stained with TUNEL in pictures a, b, c, d and e; non-apoptotic sperms are seen to be blue stained with TUNEL in pictures a, b, c, d and e.

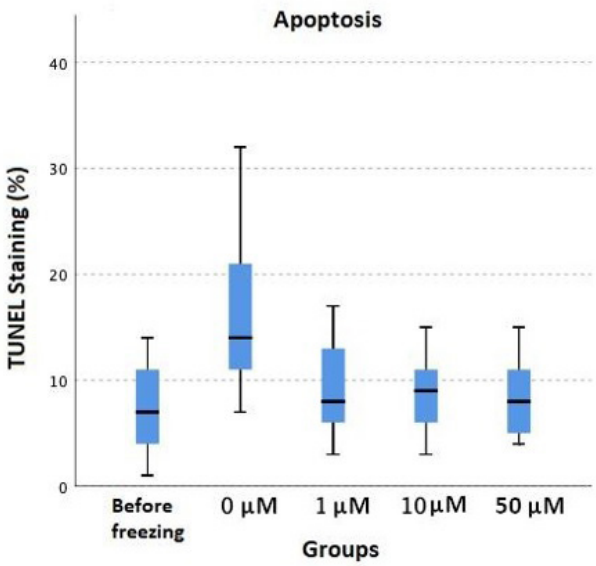

Figure 6. Pre-cryopreservation and post-cryopreservation apoptotic sperm values of the related groups.

DISCUSSION

Due to the small number of studies on how antioxidants that target mitochondria affect the freezing of sperm, this study looked at the role of different Mito-TEMPO concentrations in the freezing of human sperm. After freezing, the effects of Mito-TEMPO on the movement, shape, viability, chromatin integrity, and changes that look like apoptosis were studied. Viability and mitochondrial activity were found to decrease in sperms after freezing, and overall sperm motility was found to decrease in groups. Mito-TEMPO, on the other hand, significantly kept sperm mitochondrial activity and reduced the number of damaged mitochondria during incubation. This is likely because Mito-TEMPO goes straight to mitochondria and removes superoxide anions from mitochondria. Mito-TEMPO did not change the percentage of cells with normal shape in any of the groups. Mito-TEMPO may not have had any effect on the shape of normal and abnormal sperm because it was happened at the stage of spermatogenesis. The results of the morphology test agree with studies that say antioxidants don't change the shape of sperm in any way (10,14,15).

Cryopreservation is a key technique that is often used to keep men's ability to have children (5) and to store sperm in a stable way for a long time. Chemotherapy, radiotherapy, and surgery are all good ways to keep fertilization going before infertility interventions. Even though semen cryopreservation has made great strides in recent years, the damage caused by freezing still happens, and the quality of sperms decreases during the freezing-thawing process (16) During the cryopreservation process, oxidative stress is caused by an imbalance between ROS production and antioxidant mechanisms. Sperm cells are especially vulnerable to oxidative stress (8). When sperm is frozen, apoptotic pathways are also turned on, and ROS concentrations go up. When the amount of ROS in the body goes up, it damages the DNA of sperm and makes it harder for them to fertilize eggs. During cryopreservation, ROS are made, which changes the sperm's mitochondrial membrane potential (6). Cryopreservation changes how sperm membrane lipids are made, how long they live, and how they move. It also damages DNA in humans. Cryopreservation has a big effect on how well sperm move (17). Cryoprotectant solutions are used to lessen the stress that freezing causes. But at high concentrations, cryoprotectants are very bad for cells (4). So, cryopreservation methods need to be improved to make freezing protocol more effective (18). A lot of studies have shown that adding antioxidants to the process of freezing sperm can improve the quality of sperm that has been frozen and thawed in different ways (19–21). But there are still not enough good antioxidants (16).

Sperm endogenous antioxidants naturally neutralize ROS; however, the amount of these antioxidants decreases since seminal plasma is removed during the freezing-thawing process. For this reason, freezing medium containing supplement exogenous antioxidants is an effective method to overcome the negative effects of ROS (22,23).

While some antioxidants improve sperm functions, some may be insufficient. Antioxidants like Vitamin C, Vitamin E, catalase, quercetin, pentoxifylline, genstein, biotin, resveratrol, honey, and L-carnitine are commonly used (2).

Researchers have recently been interested in new types of antioxidants that target the mitochondria because they have many uses, work well, and don't harm the body. They have become possible ways to keep sperm from getting damaged by the stress of being frozen (24). Mitochondria is an important organelle for cell energy metabolism that modulates redox mechanism, cell development and death (9). Spermatozoa get energy for their metabolism from mitochondria through ATP synthase and oxidative phosphorylation. But they are sensitive to changes in temperature and the amount of reactive oxygen species (ROS). This makes it hard for ATP to move and lowers the quality of sperm. Its imbalance in getting rid of and making free radicals causes oxidative shock, which damages DNA and causes the cell to die (10,25). Motility, plasma membrane function, acrosome integrity, and overall viability all go down after thawing. After thawing, mobility has been said to drop from 50.6% to 30.3%. But the process by which motility goes down hasn't been fully explained yet (2).

Mito-TEMPO is an antioxidant that works on mitochondria and is a powerful ROS scavenger (26). This chemical is made by putting together tempo and triphenylphosphonium (TPP+). Tempo acts like superoxide dismutase, but while dismutase is a superoxide in the catalytic cycle, TPP is a cation that moves from the cell membrane to the cell interior (25).

This combination makes a compound that works well to remove superoxide from the mitochondria. Mito-TEMPO is also expected to keep the quality of human spermatozoa that have been frozen and then thawed (27,28). Weidinger et al. found that Mito TEMPO decreased the expression of nitric oxide synthase in the liver, as well as markers of liver and kidney damage (aspartate aminotransferase and alanine aminotransferase) (urea and creatinine) (27). Mito-Tempo is a good mitochondria-targeted antioxidant. Because it has a positive charge, it can build up 500 times in the mitochondrial matrix. It has a targeted antioxidant effect by stopping or slowing the production of mitochondrial free oxygen radicals and lipid peroxidation (24). Studies have also shown that Mito-TEMPO protects against diseases like heart damage (29), kidney damage (30), liver damage (9), Alzheimer's disease (31), sepsis models (32), Parkinson's disease (33), diabetes (34), ischemic brain disease (35), testicular toxicity (36), gastrointestinal system (37), and spinal cord damage (38).

Mito-TEMPO has been shown to improve mitochondrial function in porcine oocyte (39) and human spermatozoa (16) via decreasing oxidative stress. Seok et al. investigated the effects of different concentrations of Mito-TEMPO (0, 0,5, 5, 50 and 500 μM) on the motility of frozen-thawed porcine sperms. They proved that Mito-TEMPO addition had a beneficial effect on the motility of pig sperms (40). In another study, Kumar et al. added 50 μM Mito-TEMPO and 50 μM acetovanillone to freezing solution of buffalo sperm. When they examined semen samples in terms of progressive motility, plasma membrane integrity, lipid peroxidation, total antioxidant capacity, mitochondrial membrane potential and ROS, they reported that their separate or combined use affected the results positively (8).

In a study they conducted, Esmaeilkhanian et al. examined the efficiency of Mito-TEMPO (0, 1, 10,100 and 1000 μM) on post-thawing goat sperm quality. After thawing, they evaluated sperm mitochondria membrane potential, viability, apoptotic like changes and ROS concentration and they found that Mito-TEMPO (10 and 100 μM) improved sperm viability and reduced apoptotic like changes and ROS concentration when compared with other groups (22).

In a study they conducted on ram sperm, Zarei found that using Mito-TEMPO (0, 0.5, 5, 50 and 500 μM) improved thawed sperm motility parameters, membrane functionality, abnormal morphology, mitochondrial activity, acrosome integrity, DNA fragmentation, ROS concentration, viability and apoptotic like changes. According to the results, the efficiency of 5 and 50 μM Mito-TEMPO was found to be higher when compared with the other groups. In addition, apoptotic like changes were found to be lower in groups that were given lipid peroxidation and ROS concentration 5 and 50 μM Mito-TEMPO (10).

In a study they conducted on Verasfer variegatus, Zidni et al. froze sperms with different concentrations of Mito-TEMPO (0, 25, 50, 75, 100, 125, 150, 175 and 200 μM) and evaluated the post-thawing quality of sperms. When compared with control groups, antioxidant supplementation in sperm was found to be more effective in increasing post-thawing motility, maintaining cellular survival rates and preventing the increase in DNA damage that occurs in sperms during storing (7).

Zhang et al. found that in human sperm cryopreservation, Mito-TEMPO concentrations between 0 and 50 Mm showed significant improvement in post-thawing sperm motility, viability, membrane activity and mitochondrial membrane potential. They stated that adding Mito-TEMPO (10 and 100 μM) to cryopreservation solution improved sperm membrane integrity, mitochondrial membrane potential and chromatin integrity. They also found that Mito-TEMPO decreased the formation of oxidative stress and prevented mitochondria and DNA damage during cryopreservation (24).

In a study they conducted, Lu et al. stored semen samples by freezing them with diluents including different concentrations (0.0, 0.5, 5, 50 and 500 μM) of Mito-TEMPO. Sperm motility, viability, membrane integrity, mitochondrial membrane potential and antioxidant activities were measured. The results showed that adding Mito-TEMPO (5–50 μM) significantly increased post-thawing sperm motility, viability, membrane integrity and mitochondrial membrane potential. In the meantime, antioxidant enzyme activities increased and MDA content decreased in the group supplemented with Mito-TEMPO (16).

Asadzadeh et al. looked at the effects of Mito-TEMPO on ram sperm quality and fertility potential during the freezing-thawing process. They found that adding 5 μM and 50 μM Mito-TEMPO to semen samples led to higher post-thawing sperm motility, acrosome integrity, and viability, as well as lower lipid peroxidation and late apoptotic-like changes (25).

CONCLUSION

Using Mito-TEMPO improved deteriorated human sperm parameters during the thawing process. The damage that occurs during cryopreservation as a result of Mito-TEMPO effect can be prevented. Therefore, it can be said that adding Mito-TEMPO in diluent while thawing is an effective method in improving post-thawing sperm quality. In addition, more research is needed to investigate whether sperm fertilization, embryo implantation and pregnancy are affected. Further studies may help to clarify the mechanisms underlying protective role of Mito-TEMPO.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Analysis of the Relationship Between Serum Zinc Values and Allergic Rhinitis Parameters in Patients with Allergic Rhinitis

Alerjik Rinitli Hastalarda Serum Çinko Değerleri ile Alerjik Rinit Parametreleri Arasındaki İlişkinin Analizi

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Abstract

Background/Aim: Zinc is an significant trace element that acts an active part in the immune system and is associated with allergic inflammatory diseases. In the literature, various results have been shown in studies on the coexistence of serum zinc level and allergic rhinitis. The objective of this research was to analyze the intercourse among serum zinc levels and whole blood parameters in allergic rhinitis (AR).

Method: In this research, patients were appraised in consistency with the instruction for "Allergic Rhinitis and Its Effect on Asthma". Serum total Ig E, C-reactive protein grades in the AR group and leukocyte, neutrophil, eosinophil and lymphocyte counts, neutrophil/lymphocyte, eosinophil/lymphocyte, platelet/lymphocyte ratio and serum zinc values in whole-blood parameters of all cases were analyzed and contrasted between the AR and control groups.

Findings: Neutrophil and eosinophil counts and eosinophil/lymphocyte ratio were presented as significantly superior in the AR category than in the control category ($p<0.05$). Serum zinc values in the AR category were remarkably underneath than those in the control category ($p<0.05$). In the univariate model, it was noticed that the eosinophil and zinc values had a significant-independent differential effect in distinguishing the AR and control category patients ($p< 0.05$).

Conclusion: Serum zinc level, neutrophil and eosinophil count, eosinophil/lymphocyte ratio in the blood are practical biochemical indicators that can be used to recognition, treatment, together with following-up of cases with allergic rhinitis. It is assumed that with the support of zinc deficiency, important clinical benefits can be achieved in anti-allergic treatment.

Keywords: Rhinitis, allergic, trace elements, skin tests

Özet

Giriş/Amaç: Çinko, bağışıklık sisteminde aktif rol oynayan, alerjik inflamatuar hastalıklarla ilişkili önemli bir eser elementtir. Literatürde serum çinko düzeyi ile alerjik rinit hastalığının birlikteliği konusunda yapılan çalışmalarda farklı sonuçlar gösterilmiştir. Bu çalışmanın amacı, alerjik rinitte serum çinko seviyeleri ile tam kan değerleri arasındaki ilişkiyi araştırmaktır.

Yöntem: Alerjik rinit tanısı alan erişkin yüz otuz iki kişi hasta ve yüz otuz altı kişi sağlıklı kontrol grubu olarak incelenmiştir. Hastalar "Alerjik Rinit ve Astım Üzerindeki Etkisi" kılavuzuna göre değerlendirilmiştir. Hasta grubunda serum total IgE, C reaktif protein düzeyleri ile tüm olguların tam kan parametrelerinde lökosit, nötrofil, eozinofil ve lenfosit sayıları, nötrofil lenfosit, eozinofil lenfosit, platelet lenfosit oranı ve serum çinko değerleri incelenmiş, hasta ve kontrol grubu arasında karşılaştırılmıştır.

Bulgular: Hasta grubunda nötrofil ve eozinofil sayısı, eozinofil lenfosit oranı kontrol grubundan kayda değer ölçüde daha yüksek bulunmuştur ($p<0.05$). Hasta grubunda serum çinko değeri kontrol grubundan anlamlı olarak daha az tespit edilmiştir ($p<0.05$). Tek değişkenli modelde vaka ve kontrol grubu hastalarını ayırmada eozinofil, çinko değerinin anlamlı-bağımsız ayırıcı etkisi olduğu gözlenmiştir ($p< 0.05$).

Sonuç: Çinko, alerjik rinitte inflamasyonda rol alan önemli bir eser elementtir. Serum çinko düzeyi, kanda nötrofil ve eozinofil sayısı, eozinofil lenfosit oranı alerjik rinit hastalarında tanı, tedavi ve takipte kullanılabilecek pratik biyokimyasal göstergelerdir. Çinko eksikliğinin desteklenmesi ile anti alerjik tedavide önemli klinik faydalar sağlanılabileceği düşünülmektedir.

Türkçe Anahtar Kelimeler : Rinit, alerjik, eser elementler, deri testleri

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INTRODUCTION

Allergic rhinitis (AR) is an important global health problem. AR is one of the common complaints for applying to the otolaryngology (ENT) outpatient clinic. The mean prevalence of AR is about 18.1% (1%-54.5%) in the general population (1, 2).

It is known that systemic inflammation takes place in addition to nasal inflammation in AR pathogenesis. It is characterized by local collection of inflammatory cells such as; T-lymphocyte, mast cells, eosinophils, basophils, besides neutrophils in blood and tissue (3). AR results from immunoglobulin-E (IgE)-mediated reactions to inhaled allergens. It is a common chronic disease worldwide (4).

AR has a negative effect on daily activity, school performance, and academic achievement. It is also known to reduce the quality of life by causing a loss of workforce and sleep disorders (5).

The main symptoms of AR are rhinorrhea, nasal itching, sneezing, and nasal congestion. Rhinorrhea is usually profuse and serous in nature. Paroxysmal sneezing attacks are the most characteristic symptoms of AR and are accompanied by nasal itching and irritation (6). In the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline, AR is classes as intermittent or persistent and mild or moderate/severe. Determination is bottomed on the practical records together with physical examination. In cases who have uncontrollable rhinitis or long-term symptoms despite medications, skin prick tests to identify the allergen or the presence of specific IgE antibodies against the allergen should be examined (4).

IgE has a main act in type I hypersensitivity, which reflects the sensitivity of mast cells by allergen-specific IgE antibodies bound to their high-affinity receptors (FcεRI) (7). Zinc (Zn) has numerous physiological functions. It is an prominent trace element that performs an significant act in the immune tract. Zn influences many perspectives of immune task, including thymic improvement and the actions of immune cells. Zn is also related in several steps of FceRI-induced mast cell activation required for degranulation and cytokine production. It has been indicated to impede the production and mRNA expression of inflammatory cytokines. Zn is known to task as an antioxidant and stabilize cell membranes. It has been stated that Zn has an important function in allergic inflammation (8, 9). This relationship among reduced Zn levels and asthma and atopic dermatitis has been more clearly demonstrated (10, 11).

Measurement of complete blood count parameters in AR patients is cost-effective and easy to perform. Recently, there has been a tendency to use eosinophil, lymphocyte, and neutrophil ratios instead of numerical values. Neutrophil/lymphocyte ratio (NLR), eosinophil/lymphocyte ratio (ELR), and platelet/lymphocyte ratio (PLR) can be computed easily (12).

Few studies have been directed on the role of mark elements in AR disease together with they have reported contradictory outcomes. Since different results have been reported in various studies, further studies are needed. In the textes, the number of studies on the relationship among serum total IgE and Zn levels is very scarce, and there is no study on the correlation between NLR, ELR and PLR, and Zn levels.

This research aims to investigate the intercourse among serum Zn and serum total IgE grades, blood neutrophil, eosinophil and lymphocyte counts, NLR, ELR, and PLR in AR.

MATERIAL and METHODS

Study Design

Between January 2021 and September 2022, 132 patients who asked to the outpatient clinic of the Faculty of Medicine Hospital, Department of Otorhinolaryngology were contained in the investigation. Cases over the age of 18 who were diagnosed with AR and presented to the ENT outpatient clinic with objections of itching in the nose and palate, nasal congestion, nasal discharge and sneezing, whose symptoms lasted more than four weeks, and more often than four days a week and did not receive any medical treatment, were evaluated. Errors were determined according to ARIA guidelines.

In the AR group, skin prick test results, C-reactive protein (CRP) levels, serum total IgE and blood parameters of leukocyte, neutrophil, eosinophil and lymphocyte counts, NLR, ELR, PLR and serum Zn values were recorded. NLR, ELR and PLR were calculated by dividing neutrophils, eosinophils and platelets by the percentage of lymphocytes in the complete blood count analysis.

One hundred thirty-six people of similar age groups and genders who did not have AR symptoms and who were received to the medical institution due to other complaints were joined in the research as the control group.

Patients in the pediatric age group (<18) and who were recently (less than 4 weeks ago) diagnosed with AR, with a history of nasal surgery, nasal polyps, oncological diagnosis, and pregnant cases were excepted from the research.

The investigation protocol was managed in pursuance with the ethical principles in the Declaration of Helsinki and was approved by the institutional ethics committee (approval date/number 19.10.2022/10-02). The authors declared that they followed the protocols used in the study centers regarding the publication of patient data.

Zinc Levels

Serum Zn levels were measured with the brand commercial kit (Archem Diagnostics (İstanbul, TURKEY)) using colorimetric method defined in the literature. (13).

Statistical analysis

Mean, standard deviation, median minimum, maximum, frequency and ratio values were used as descriptive statistics. The distribution of variables was analyzed with the Kolmogorov-Smirnov test. The Mann-Whitney u test (in analysis of quantitative independent data), the Chi-square test (in analysis of qualitative independent data) were used. ROC curve was used to investigate the effect level and cut-off value. The effect level was analyzed with univariate and multivariate logistic regression. SPSS 28.0 (IBM Corp. Armonk NY) program was used in the analysis.

RESULTS

Patient characteristics

In the study, 132 cases with AR besides 136 control cases were evaluated. The average age was 35.5 ± 12.5 in the AR group, and 38.9 ± 14.8 in the control group. The female/male ratio was 91/41 in the AR, besides 91/45 in the control group. There was not any statistically meannig ($p > 0.05$) difference with the age and gender dispersion of the cases between the AR and control group.

The skin prick test involved positive control, negative control, tree mix, olea europeae (olive tree), cockroach, cat epithelium, weed mix, weed mix, mold mix II and mite mix allergens. Single allergen positivity was interpreted as monoallergic, and multiple allergen positivity was interpreted as polyallergic condition. The outcomes of the derm prick assays revealed 31 monoallergic and 35 polyallergic cases. The prick test was negatory in 66 cases.

With regard to the biochemistry parameters, platelet and lymphocyte values, NLR and PLR values did not differ statistically between the AR and control group ($p > 0.05$).

Neutrophil and eosinophil counts and ELR values in the AR category were statistically remarkably ($p < 0.05$) superior than the control category. Elevated serum total-IgE levels were described as > 100 kU/L. Serum total IgE was elevated in 37 patients and was within normal limits in 95 cases. The findings are represented in tables 1 and 2.

Effect of serum Zn levels on the possibility of allergic sensitization

Serum Zn values in the AR category were statistically remarkably lower than the control category ($p < 0.05$) (Table 2, Figure 1). In the univariate model, a statistically significant ($p < 0.05$) differential effect of neutrophil, eosinophil, ELR and Zn values in differentiating the cases in AR and control group was observed, while a significant-independent ($p < 0.05$) differential effect of eosinophil and Zn values was observed in the multivariate model (Table 3).

The mean serum Zn level was 81.6±14.3. There is a significant difference in serum Zn levels among the cases in the AR and control groups [The ROC analysis; Area under the curve 0.758 (0.701-0.816)], and the cut-off value was obtained as 72.6 [Area under the curve 0.694 (0.630-0.758)]. (sensitivity: 93.4%, positive prediction: 45.5%, specificity: 63.8%, and negative prediction :75.8%) (Table 4).

Relationship between serum zinc level and allergic sensitivity

Platelet, lymphocyte, eosinophil counts and ELR, PLR and CRP values didn't differ statistically between the groups with serum Zn levels < 72.6 and ≥ 72.6 ($p > 0.05$). Neutrophil counts and NLR were remarkably higher ($p < 0.05$) in the category with serum Zn level < 72.6 than in the group with ≥ 72.6. In the group with serum Zn level < 72.6, the derm prick test and serum total IgE positivity rate were statistically higher ($p < 0.05$) (Table 5).

DISCUSSION

Low serum Zn has been related with various chronic diseases. There are a few studies examining the association among Zn levels together with allergic diseases, like allergic asthma and atopic dermatitis (14). However, there are studies with different results to explain the relationship (15).

In various studies conducted in adult and pediatric age groups, AR patients and healthy control groups were compared and it was shown that serum Zn was significantly lower in the AR patient group (16-18). Conversely, there are also works demonstrations that there is no significant distinction (15).

In our research, serum Zn values were determined to be significantly under in the AR category compared to the control category.

It has been determined in various investigations that Zn has an significant role in allergic inflammatory diseases, and it has been manifested to play a act in distinct IgE-related cellular signaling cascades (19). It has been statemented that there is an imbalance in IgE-dependent immunological activities in the presence of low Zn (19). Seo et al. investigated the relationship between total IgE and serum zinc levels in AR patients and showed that serum zinc grades were low in cases with elevated serum total IgE levels, and there was a negative linear correlation between total IgE levels and zinc levels (20).

In our research, it was noticed that the total IgE level was significantly superior in the group with serum Zn level < 72.6 contrasted to the group with Zn level ≥ 72.6. Our findings promoted the investigations in the written works.

Neutrophilia is one of the systemic inflammatory markers and is associated with inflammatory diseases (21). Eosinophilic inflammation is a common feature in allergic diseases. The eosinophil count is used to state the intensity of allergic diseases. In their research, Li et al. statemented that the eosinophil count and serum total IgE level were higher in patients with AR (22).

NLR and ELR are simple biochemical parameters that can be easily performed in the detection of inflammatory and infectious illnesses (21, 23). Yenigün et al. showed that NLR and ELR values increased as a result of the systemic inflammatory reply in nasal polyposis disease (21). In their study on children with functional dyspepsia, an inflammatory disease, Savas et al. pointed out a statistically significant distinction in NLR values between the control and the AR group. Although there was numerical distinction in serum Zn levels among the groups, it was not statistically significant (24).

In a research by Kant et al., eosinophil counts and ELR quantities were noticed to be remarkably higher and NLR values lower in AR cases matched to the healthful ones (25). Göker et al. found higher NLR and PLR values in AR patients matched to the healthful group (26).

In our investigation, neutrophil and eosinophil levels were higher in the AR group. Serum Zn levels and ELR values were found to be effective in differentiating the AR and control groups. In multivariate logistic regression analysis, eosinophil count and Zn levels were found as significant independent discriminative variables. These results support that Zn levels and eosinophilia are parameters associated with AR.

This investigation has some limitations. It is uncertain whether a individual evaluation of serum Zn level exactly matches the actual serum Zn level in the population.

Since it was not checked whether there was an improvement in AR patients after Zn deficiency treatment, obvious information could not be acquired about the role of Zn deficiency in the intensity and treatment of the disease.

Knowledge on the act of serum total IgE as a marker in AR intensity and diagnosis is restricted and changeable. This issue should be addressed further.

Failure to look at the correlation of allergen-specific IgE with Zn level created a limitation in the specificity of the study.

CONCLUSION

Zn is a crucial trace element involved in the definition of the severity and therapy of chronic inflammatory diseases. The low serum Zn levels detected in AR patients in our study support the facts of other investigations in the literary texts. Morover, the association between neutrophilia, eosinophilia, high ELR, low Zn levels and AR indicates that a low Zn level might be associated with AR disease. Checking the serum Zn concentration is beneficial in the aftercare and therapy of AR disease, and we trust that it may be a useful strategy for advancing anti-allergy treatments.

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TABLES

Table 1. Demographic data of the entire cohort

		Min-Max	Median	Mean ± sd/ n (%)
Age		18.0 - 84.0	34.0	37.2 ± 13.8
Gender	Female			182 (67.9%)
	Male			86 (32.1%)
Platelet (x10³)		79.0 - 532.0	272.0	279.7 ± 68.8
Neutrophil (x10³)		0.97 - 9.00	3.89	4.13 ± 1.38
Lymphocyte (x10³)		0.78 - 42.50	2.22	2.56 ± 2.75
Eosinophil (x10³)		0.00 - 1.85	0.16	0.22 ± 0.21
NLR		0.58 - 6.81	1.70	1.88 ± 0.79
ELR		0.00 - 0.95	0.07	0.10 ± 0.10
PLR		1.0 - 475.2	119.9	125.1 ± 45.9
CRP		0.10 - 2.00	0.10	0.19 ± 0.25
Zinc		43.2 - 143.8	79.9	81.6 ± 14.3
Prick Test	Non			66 (50.0%)
	Mono			31 (23.5%)
	Poly			35 (26.5%)
Total IGE	High			37 (28.0%)
	Normal			95 (72.0%)
Rhinitis				132 (49.3%)
Healthy controls				136 (50.7%)

Table 2. Comparison of AR and control groups

		AR Group		Control Group		p
		Mean ± sd/ n(%)	Median	Mean ± sd/ n (%)	Median	
Age		35.5 ± 12.5	34.0	38.9 ± 14.8	35.5	0.080 [m]
Gender	Female	91 (68.9%)		91 (66.9%)		0.722 [χ²]
	Male	41 (31.1%)		45 (33.1%)		
Platelet (x10³)		286.5 ± 63.9	276.5	273.0 ± 72.7	265.0	0.052 [m]
Neutrophil (x10³)		4.32 ± 1.35	4.10	3.94 ± 1.40	3.62	***0.013*** [m]
Lymphocyte (x10³)		2.67 ± 3.55	2.29	2.45 ± 1.63	2.19	0.363 [m]
Eosinophil (x10³)		0.26 ± 0.25	0.17	0.18 ± 0.15	0.15	***0.003*** [m]
NLR		1.92 ± 0.71	1.75	1.84 ± 0.87	1.60	0.102 [m]
ELR		0.11 ± 0.12	0.08	0.08 ± 0.07	0.06	***0.005*** [m]
PLR		124.2 ± 38.8	119.6	125.9 ± 52.0	120.1	0.530 [m]
Zinc		75.7 ± 12.8	74.1	87.4 ± 13.4	86.8	***<0.001*** [m]

[m] Mann-Whitney u test / [χ²] Chi-Square test

Table 3. Evaluation of the effectiveness of laboratory parameters with Univariate and Multivariate analysis

	Univariate Model			Multivariate Model		
	OR	%95 CI	p	OR	%95 CI	p
Neutrophil	1.22	1.02 - 1.46	***0.027***			
Eosinophil	10.76	2.33 - 49.63	***0.002***	11.21	2.14 - 58.65	***0.004***
ELR	58.22	2.42 - 1403.7	***0.012***			
Zinc	0.928	0.906 - 0.950	***<0.001***	0.927	0.904 - 0.950	***<0.001***
Logistic Regression (Forward LR)						

Table 4. Evaluation of the effectiveness of serum zinc level in separating AR and control groups by ROC analysis

	Area under the curve	%95 Confidence Interval	p
Zinc	0.758	0.701 - 0.816	***<0.001***
Zinc Cut Off Value 72.6	0.694	0.630 - 0.758	***<0.001***

		Control Group	AR Group		%
Zinc	< 72.6	60	9	Sensitivity	93.4%
	≥ 72.6	72	127	Positive Prediction	45.5%
				Specificity	63.8%
				Negative Prediction	87.0%

Table 5. Comparison of AR patients according to serum zinc ≥ 72.6 cut off value

		Zinc < 72.6		Zinc ≥ 72.6		p
		Mean ± sd/ n (%)	Median	Mean ± sd/ n (%)	Median	
Age		36.2 ± 14.2	33.0	37.6 ± 13.7	35.0	0.326 [m]
Gender	Female	55 (79.7%)		127 (63.8%)		***0.015*** [χ²]
	Male	14 (20.3%)		72 (36.2%)		
Platelet (x10³)		286.3 ± 70.1	273.0	277.4 ± 68.3	271.0	0.333 [m]
Neutrophil (x10³)		4.60 ± 1.33	4.40	3.97 ± 1.37	3.69	***<0.001*** [m]
Lymphocyte (x10³)		2.25 ± 0.59	2.19	2.66 ± 3.16	2.25	0.341 [m]
Eosinophil (x10³)		0.24 ± 0.23	0.16	0.21 ± 0.21	0.16	0.892 [m]
NLR		2.19 ± 0.96	1.95	1.77 ± 0.69	1.60	***<0.001*** [m]
ELR		0.11 ± 0.10	0.07	0.09 ± 0.10	0.07	0.469 [m]
PLR		134.7 ± 53.9	126.0	121.7 ± 42.4	117.0	0.062 [m]
CRP		0.20 ± 0.30	0.10	0.18 ± 0.20	0.10	0.666 [m]
Zinc		65.5 ± 5.7	66.1	87.2 ± 12.0	85.1	
Prick Test	Non	20 (33.3%)		46 (63.9%)		***0.001*** [χ²]
	Mono	22 (36.7%)		9 (12.5%)		
	Poly	18 (30.0%)		17 (23.6%)		
Total IgE	(+)	25 (41.7%)		12 (16.7%)		***0.001*** [χ²]
	(-)	35 (58.3%)		60 (83.3%)		

FIGURES

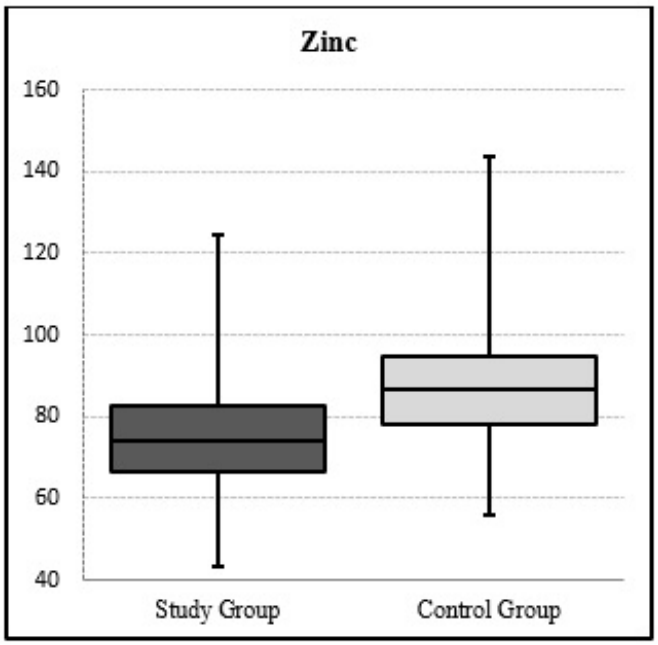

Figure 1. Evaluation of the effectiveness of serum zinc level in separating AR and control groups by ROC Cure

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The Relationship Between Daily Physical Activity And Motor Proficiency In 8–10 Years Old Amateur Children Athletes

8-10 Yaş Grubu Amatör Sporcu Çocuklarda Günlük Fiziksel Aktivite İle Motor Performans Arasındaki İlişki

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Abstract

Purpose: The purpose of this study is to examine the relationship between motor proficiency and physical activity in 8- to 10- year old amateur children athletes.

Methods: A total of 87 volunteer amateur athletes, consisting of 50 girls and 37 boys with a mean age of 9.18±0.8 years, participated in the research. Children's demographic data were recorded, and physical activity level was assessed by Bouchard's Physical Activity Record. Motor proficiency was determined by Bruininks Oseretsky Test of Motor Proficiency (BOTMP) which assess gross and fine motor skills with 8 headlines.

Results: The 8 subtests assess motor proficiency, three of them were significantly associated with daily energy expenditure. Upper Limb Coordination Tests [Catching a tossed ball with two hands p=0.001; r=0.399), Throwing a Ball at a Target With Dominant Hand (p=0.016; r=0.303)] and daily energy expenditure were assigned associated significantly on positive way. Daily energy expenditure and reaction time were found associated significantly on negative way (p=0.023; r=-0.286).

Discussion: In results; it's seen that children's motor proficiency is positively associated with physical activity and negatively associated with sedentary lifestyle. Due to the fact that motor performance is a determinant parameter in terms of physical activity, it was concluded that focusing on increasing motor skills from childhood onwards is an effective strategy for improving the physical activity and health of the child in the youth and adult periods.

Key words: Physical Activity, Motor Proficiency, Amateur Children Athletes

Özet

Amaç: Bu araştırmanın amacı, 8-10 yaş grubu amatör sporcu çocuklarda fiziksel aktivite ile motor performans arasındaki ilişkinin belirlenmesidir.

Yöntem: Araştırmaya yaş ortalaması 9.18±0,8 yıl olan 50 kız, 37 erkek toplam 87 amatör gönüllü sporcu katıldı. Çocukların demografik bilgileri kaydedildi ve fiziksel aktivite düzeyleri "Bouchard'ın Fiziksel Aktivite Kaydı" ile değerlendirildi. Motor performansları ise sekiz alt başlıkta kaba ve ince motor becerileri değerlendiren "Bruininks Oseretsky Motor Performans Testi (BOTMP)" ile belirlendi.

Bulgular: Motor performansı ölçen 8 alt testten üçünde motor performans ile günlük enerji tüketimi arasında anlamlı ilişki vardı. Üst ekstiremitelerin koordinasyonu testleri [Fırlatılan Topu Her İki El ile Yakalama (p=0.001; r=0.399), Dominant El ile Topu Hedefe Fırlatma (p=0.016; r=0.303)] ile günlük enerji tüketimi arasında pozitif yönde anlamlı ilişki saptandı. Günlük enerji harcama tüketimi ile reaksiyon zamanı arasında ise negatif yönde anlamlı ilişki bulundu (p=0.023; r=-0.286).

Tartışma: Araştırmanın sonucunda; çocuklarda motor performansın fiziksel aktivite ile pozitif yönde, sedanter yaşam şekli ile negatif yönde ilişkili olduğu görüldü. Motor performansın fiziksel aktivite açısından belirleyici bir parametre olması nedeniyle bireylerde çocukluk döneminden itibaren motor becerileri arttırmaya odaklanılmasının, çocuğun genç ve erişkin dönemlerindeki fiziksel aktivite ve sağlığını geliştirme hedefine yönelik etkin bir strateji olduğu görüşüne varıldı.

Anahtar Sözcükler: Fiziksel Aktivite, Motor Performans, Amatör Sporcu Çocuklar

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INTRODUCTION

Today's technologies make life easier, causing a noticeable decrease in children's exercise habits and serious health problems (1). Individuals who spent their childhood physically active are less likely to encounter these problems than those who are not active. Therefore, it is necessary to look for the cause and solution of the problem in childhood habits (2-4).

Between the ages of two and seven, children acquire basic motor skills such as running, jumping, bouncing, catching, throwing, and kicking a ball. These skills are considered fundamental because they are necessary for daily life and are commonly found in all children (5). Depending on age and gender, basic motor skills are acquired with the maturation of the neuromuscular system. The neural structures of children between the ages of six and eight are close to those of adults. Acquiring basic motor skills enables purposeful action later in life. Apart from moving in space, human easily overcomes obstacles and uses objects effectively (6, 7). Children with weak motor skills may turn to sedentary life by avoiding the physical obstacles they encounter during the day. Adequate and balanced nutrition and regular physical activity should be made a habit in childhood in order to prevent health problems caused by sedentary life and to increase health status and quality of life in adulthood (8). Since today's children will be the healthy adults of tomorrow, specific physical activity programs should be designed and expanded for them. Developing and implementing strategies to support children's health should also be other goals (9).

Based on these considerations, our research was planned to determine whether there is a relationship between children's daily physical activities and their motor performance, including basic motor skills, and to form a model for programs to be developed for the protection and development of lifelong health in the light of the results. In this context, the effect of daily physical activity on motor performance in amateur children athletes aged 8–10 years was investigated.

METHODS

Participants

The research was carried out in a sports club, which is affiliated to Bornova District of İzmir province In this cross-sectional study children who were registered to a sports club and had written permission from their parents were included. Inclusion criteria for amateur children athletes; being between the ages of 8-10, participating in sports activities at least 2 days a week, be interested in a sport as an amateur for at least one year, and volunteering to participate in the study is provided by both the family/ guardian and the child. The exclusion criteria for amateur children athletes; the presence of a known cardiac, neurological or orthopedic health problem, a history of neuromuscular injury in the last 6 months, pain during the evaluation, and not volunteering to participate in the study. Before starting the study, participants were informed about the study and signed the volunteer form parental consent forms indicating that they participated voluntarily. Necessary permissions were obtained from the Dokuz Eylul University Faculty of Medicine Clinical and Laboratory Research Ethics Committee (No: 26.12.2008/448).

Measurements

SDemographic information of all children participating in the study was recorded, daily physical activity level and motor performance were measured. Daily physical activity level was measured using Bouchard's Physical Activity Record Questionnaire, and motor performances were measured using the Bruininks-Oseretsky Motor Test Battery. These methods are valid and reliable methods. (10-12).

Physical Activity Level

The daily physical activity levels of the cases were determined using the "Bouchard's Physical Activity Record" questionnaire. In the survey; there are 5 columns, in the 1st column there are numbers from 0 to 23 representing the hours of the day, and next to the hours there are 4 columns that represent 1/4 of an hour as 0–15, 15–30, 30–45, 45–60 . With the help of their parents, the subjects marked the activity code that was appropriate for the activity they did in a 15-minute period, taking into account the scale on the front page of the questionnaire. Subjects were asked to fill in this table for 3 days in a week; It was reminded that two of these three days should be weekdays and one should be weekends (11).

Evaluation of Motor Performance

In the research, the short form "Bruininks-Oseretsky Motor Test Battery" was used to evaluate the motor performance of children. The Bruininks-Oseretsky Motor Test Battery consists of eight subtests such as running speed/agility, balance, bilateral coordination, strength, upper extremity coordination, reaction time, visual motor control, and upper extremity speed/skill (10, 12).

Statistical analysis

The data obtained in the evaluation were analyzed by the 'SPSS for Windows 20.0' program. Microsoft Office Excel 2003 program was used to calculate daily energy consumption and physical activity score. The relationship of the evaluation parameters with each other was interpreted by Pearson Correlation Analysis in parametric conditions and Spearman Correlation Analysis in non-parametric conditions. Significance level was accepted as $p<0.05$.

RESULTS

Table 1. Descriptive statistics of participants' demographic characteristics, motor performance and physical activity measurements

		Min.	Max.	Mean	SD
	Age (years)	8	10	9.18	0.80
	Height (cm)	120	161	142.43	8.54
	Weight (kg)	23	65	36.89	7.81
	BMI (kg/m²)	13.39	26.89	18.09	2.86
Running speed/agility	Running Speed Agility (s)	6.54	9.58	7.87	0.59
Balance	Standing on a Dominant Foot on the Balance Board (s)	3	10	9.02	2.10
	Forward Heel-Toe Walk on Balance Board (step)	3	6	5.72	0.71
Bilateral coordination	Alternately Raising and Lowering the Feet while Circling the Fingers	0	1	0.03	0.18
	Knocking Hands While Jumping with Two Feet (applause)	1	3	2.31	0.57
Strength	Standing Long Jump (cm)	73	161	116	17.85
Upper extremity coordination	Catch the Thrown Ball with Both Hands (shot)	3	5	4.63	0.64
	Throwing the Ball at the Target with the Dominant Hand (hit)	1	5	3.51	1.15
Reaction time	Reaction Time (cm)	12	30	22.64	4.15
Visual motor control	Dominant Manual Line Drawing Along Straight Line (error)	0	5	1.89	1.29
Upper extremity speed/skill	Distinguish Colored Cards with Dominant Hand (card)	9	23	14.54	2.64
	Dominant Manual Dotting in Circles (point)	17	40	26.64	5.58
Daily Physical Activity Level	Daily Energy Consumption (kcal)	487.20	2644.04	1486.02	6.71
	Physical Activity Score	0.55	2.56	1.79	0.01

SD: standard deviation

Fifty girls and 37 boys, total 87 volunteer amateur children athletes who have the mean age 9.18±0.8 years were participated the research. Demographic characteristics of the participants, descriptive statistics of motor performance and physical activity measurements are shown in Table 1. In addition, when the relationship between motor performance and physical activity level of amateur children athletes are examined; A significant correlation was found between daily energy consumption and upper extremity coordination and reaction time (respectively; $p<0.05$, r:0.399; $p<0.05$, r:0.303, $p<0.05$, r:-0.286). A significant correlation was found between physical activity score and running speed agility, balance, strength, upper extremity coordination, reaction time and upper extremity speed agility (respectively, $p<0.05$, r:-0.320; $p<0.05$, r:0.277, $p<0.05$, r:-0.267, $p<0.05$, r:0.296, $p<0.05$, r:-0.270, $p<0.05$, r:0.303) Table 2.

Table 2. The relationship between motor performance and physical activity level of amateur children athletes

			Daily Energy Consumption (kcal)	Physical Activity Score
Running speed/agility	Run Speed Agility (s)	r	-0.028	**-0.320***
		p	0.828	**0.011**
Balance	Dominant Standing on Balance Board (s)	r	-0.142	0.173
		p	0.266	0.174
	Forward Heel-Toe Walk on Balance Board (step)	r	0.048	**0.277***
		p	0.711	**0.028**
Bilateral coordination	Alternately Raising and Lowering the Feet while Circling the Fingers	r	-0.085	-0.025
		p	0.510	0.846
	Knocking Hands While Jumping with Two Feet (applause)	r	0.211	-0.220
		p	0.098	0.083
Strength	Standing Long Jump (cm)	r	0.085	**0.267***
		p	0.507	**0.034**
Upper extremity coordination	Catch the Thrown Ball with Both Hands (shot)	r	**0.399***	0.097
		p	**0.001**	0.451
	Throwing the Ball at the Target with the Dominant Hand (hit)	r	**0.303***	**0.296***
		p	**0.016**	**0.019**
Reaction time	Reaction Time (cm)	r	**-0.286***	**-0.270***
		p	**0.023**	**0.032**
Visual motor control	Dominant Manual Line Drawing Along Straight Line (error)	r	-0.114	-0.136
		p	0.375	0.287
Upper extremity speed/skill	Distinguish Colored Cards with Dominant Hand (card)	r	0.177	-0.236
		p	0.164	0.063
	Dominant Manual Dotting in Circles (point)	r	0.224	**0.303***
		p	0.077	**0.016**

*p<0.05, r: correlation coefficient

DISCUSSION

In this study examining the relationship between daily physical activity and motor performance in amateur children athletes aged 8-10 years, daily energy consumption and physical activity scores were found to be associated with many variables of motor performance.

Looking at the literature, Williams et al. found that children with poor motor performance were less active than children with high motor performance in a study of 3 and 4 years old preschool children (13). In addition, Wrotniak et al. reported that motor skills were positively related to physical activity and inversely related to sedentary activity in children aged 8 to 10 years (14).

The study by İbiş et al. in 2021, found that there is a positive and significant relationship between physical activity level and locomotor skills (15). In our study, parallel to the literature, a positive relationship was found between upper extremity motor coordination and daily energy consumption, and a significant relationship was found between physical activity score and running speed, agility, balance, strength and reaction time. Accordingly, it can be concluded that there is a relationship between daily physical activity and motor performance in sports children aged 8-10 years. Our study, unlike the previous studies with these variables, was carried out on athletic children. Thanks to this research, it can be stated that the relationship between physical activity and motor performance seen in non-athletes is also valid in children who are athletes. Physical activity has been associated with health in many previous studies and physical activity is used to promote health (16). According to the results of this research, we can say that strategies to improve motor performance can be used in addition to physical activity in improving health.

Balance means maintaining body position without external help. Balance is an integral part of motor activity and motor skills in children. Roncesvalles et al. stated that balance development begins in the first year of life and continues until the ninth year (17). Stanek et al. investigated balance, weight, height and physical activity level in children aged 7-9 years. As a result of the study, they concluded that balance develops with age in children, physically active children have better balance results than inactive children, and the number of participation in sports classes is not related to postural balance. (18). In another study, Pujianto et al. concluded that physical activity level in early childhood is associated with static balance (19). The results obtained from our study are in line with the literature and we found a significant relationship between some balance tests and physical activity score. We think that the reason for this may be that the proprioceptors and mechanoreceptors stimulated in the muscles and joints have improved the balance with the increase in physical activity.

The benefits of regular physical activity for the health, physical fitness, and behavior of school-age children and adolescents have been debated for years (20). When the literature is examined, the number of studies examining the relationship between motor coordination and physical activity in children is very few. Lopes et al. concluded that physical activity was a predictor of motor control in children aged 6-10 years. (21).

In our study, it was observed that there was no significant relationship between daily physical activity and some parameters of motor performance. This may be due to the fact that environmental factors can also affect engine performance. In addition, the children in our research group were basketball and volleyball players, and they were doing sport-specific training at least 2 days a week. Their sport-specific training may have resulted in better scores in some motor skills, while lowering scores in some motor skills. Therefore, there may not be a significant relationship with physical activity in all variables of motor performance. However, since these parameters can also be used to increase the level of physical activity, such activities can be emphasized in children's participation in games and sports. The positive correlation between physical activity and motor performance in our study and similar studies in the literature shows that the tests can also be taken as reference in activity program modelling. This topic can be expanded in future research by customizing it to age and gender.

CONCLUSION

According to the results of our research, it is understood that there is a positive relationship between physical activity and motor performance in amateur children athletes. Children with weak motor skills can avoid the physical obstacles they encounter during the day and switch to a more sedentary lifestyle. For this reason, not only physical activity but also motor performance and related parameters should be taken into account when carrying out studies to increase physical activity. As a result, following strategies to increase motor skills from childhood is a goal that should not be overlooked in improving the physical activity and health of the child in the youth and adolescence period.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Examination of the Effect of the Pandemic on Physical Activity and Dysmenorrhea

Pandeminin Fiziksel Aktivite ve Dismenoreye Etkisinin Birlikte İncelenmesi

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Abstract

Background: Dysmenorrhoea releated with body mass index -less than 20 kg/cm2, smoking, early menarche, longer menstrual cycles, irregular menstrual flow and a family history of dysmenorrhea. On the other hand, the relationship between physical activity level and dysmenorrhea is still controversial.

Purpose of the study: This study aimed to examinate of the effect of the pandemic on physical activity and dysmenorrhea together.

Results: Individuals' severity of dysmenorrhea, menstrual symptoms, physical activity levels were assessed with "Visual Analogue Scale (VAS)", "Menstruation Symptom Questionarre (MSQ)", "International Physical Activity Questionnaire (IPAQ)", respectively. Moreover; BMI was calculated. Assessments were carried out twice, before -during the pandemic. The VAS value was 6.23 ± 1.78 before the pandemic, it was 7.20 ± 1.63 during the pandemic. The IPAQ score was 1274.67 ± 1232.26 before the pandemic, it was 902.74 ± 892.33 during the pandemic. While the changes in VAS (t: -3.549, p: 0.001) and IPAQ (t: 2.543, p: 0.013) values before and during the pandemic were statistically significant MSQ (t: -.781, p: 0.437) and BMI (t: -.938, p: 0.351) changes were not statistically significant.

Conclusion: When the severity of dysmenorrhea and physical activity levels were compared with before the pandemic, a decrease in the level of physical activity and an increase in the severity of dysmenorrhea were found statistically significant during the pandemic ($p<0.05$). Although there was an increase in BMI and menstrual symptoms this increase wasn't statistically significant ($p> 0.05$).

Keywords: Dysmenorrhea, COVID-19, Physical Activity, Pandemic

Özet

Giriş: Dismenore, vücut kütle indeksinin (VKİ) 20 kg/cm2'den az olması, sigara kullanımı, erken menarş, daha uzun süren menstruasyon, düzensiz siklus ve ailede dismenore öyküsü ile ilişkilidir. Öte yandan fiziksel aktivite düzeyi ile dismenore arasındaki ilişki halen tartışmalıdır.

Amaç: Bu çalışmada pandeminin fiziksel aktivite ve dismenoreye etkisinin birlikte incelenmesi amaçlanmıştır.

Bulgular: Bireylerin dismenore şiddeti, menstrual semptomları, fiziksel aktivite düzeyleri sırasıyla "Vizuel Analog Skala (VAS)", "Menstruasyon Semptom Ölçeği (MSÖ)", "Uluslararası Fiziksel Aktivite Anketi (UFAA)" ile değerlendirildi. Ayrıca katılımcıların VKİ değerleri hesaplandı. Pandemi öncesinde ve döneminde olmak üzere iki kez değerlendirme yapıldı. Pandemi öncesi VAS değeri 6,23 ± 1,78 iken pandemide 7,20 ± 1,63 idi. Pandemi öncesi UFAA skoru 1274,67 ± 1232,26 iken pandemide 902,74 ± 892,33 idi. Pandemi öncesi ve pandemideki VAS (t: -3,549, p: 0,001) ve UFAA (t: 2,543, p: 0,013) değerlerindeki değişim istatistiksel olarak anlamlı iken MSÖ (t: -.781, p: 0,437) ve VKİ (t: -,938, p: 0,351) değerlerindeki değişim istatistiksel olarak anlamlı bulunmadı.

Sonuç: Pandemi öncesi ile pandemi sırasındaki dismenore şiddeti ve fiziksel aktivite düzeyleri karşılaştırıldığında, pandemi sırasında fiziksel aktivite düzeyinde azalma ve dismenore şiddetindeki artış istatistiksel olarak anlamlı bulundu ($p<0.05$). VKİ ve menstrüel semptomlarda artış olmasına rağmen bu artış istatistiksel olarak anlamlı değildi ($p> 0.05$).

Anahtar Kelimeler: Dismenore, COVID-19, Fiziksel Aktivite, Pandemi

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INTRODUCTION

Dysmenorrhea, a gynecological problem called "painful menstruation", is frequently observed in women and characterized by severe uterine pain, manifested as a cyclical pain in the lower quadrant of the abdomen during menstruation (1-3). There are two types of dysmenorrhea: primary and secondary. While primary dysmenorrhea occurs without an obvious pathological cause, secondary dysmenorrhea occurs due to pathological causes such as endometriosis and pelvic inflammatory disease (1,4-6). The pain caused by dysmenorrhea is concentrated in the pelvic region, affecting women to varying degrees, causing them to experience labor loss at work and in school (1, 7, 8). A study conducted with school-age girls reported that students' absenteeism occured due to dysmenorrhea (9). Working women are reported to experience situations such as not being able to go to work or not working with a good performance at least once a year with a rate of 5%-14% (10). Dysmenorrhea is a common problem among women both in Turkey and in other countries and affects women negatively (11).

Risk factors that affect the emergence of dysmenorrhea are reported as hormonal problems, prolonged exposure to stress, vitamin deficiencies, smoking, unhealthy eating habits and physical inactivity/sedentary lifestyle (12). Literature review points to studies which indicated that sedentary lifestyle is a risk factor for dysmenorrhea. (13, 14). Kaur et al. (2018) also concluded that physical activity is significantly effective in reducing pain and improving quality of life (15). Munuleh et al. (2018) stated that physical activity reduces the symptoms associated with dysmenorrhea (16).

Today, it is reported that physical activity is an effective approach that can be used non-pharmacologically for the prevention and treatment of dysmenorrhea (17). Physical activity has the effect of reducing renin levels and increasing estrogen and progesterone levels in women with dysmenorrhea. This change caused by physical activity reduces the physical symptoms related to dysmenorrhea and alleviates the complaints (18). According to studies, exercises that increase pelvic blood flow before menstruation delay the onset of prostaglandin accumulation in this region and facilitate the transfer of wastes from the uterus (19, 20). In addition, regular exercise plays an important role in reducing stress and increasing the level of endorphins (21). On the other hand, some studies in the liteature did not detect any relationship between physical activity level and dysmenorrhea. In their study, Maruf et al. (2013) found no relationship between physical activity and dysmenorrhea, on the other hand, Latthe et al. (2006) reported an inverse relationship. In their study on 1,127 women, Barcikowska et al. (2020) found that women with sedentary lifestyles experienced dysmenorrhea, however the frequency of physical activity did not have an effect on dysmenorrhea (22-24). Studies show that sedentary lifestyle is a risk factor for dysmenorrhea (13, 14).

In the studies carried out, the effect of physical activity in dysmenorrhea has not been clearly determined (25). However, the effects of physical activity limitation on health parameters in patients with dysmenorrhea during the pandemic are unknown. Accordingly, this study conducted to determine the effects of chancing in physical activity levels during the pandemic period on pain and menstrual symptoms in patients with dysmenorrhea.

MATERIAL AND METHODS

Type of Research

The descriptive study used quantitative research methods.

Research Sample

The sample of the study consisted of individuals between the ages of 18-27 who were diagnosed with primary dysmenorrhea by an obstetrician and gynecologist. Inclusion criteria were as follows: not being pregnant before, not using drugs that cause dysmenorrhea, and agreeing to participate in the research. The exclusion criteria were as follows having undergone any surgical intervention related to dysmenorrhea, inability to stand without support, having cardiovascular disease, having irregular menstrual cycles, continuous drug use, cancer diagnosis, and refusal to participate in the study (26). Participants who did not fill out the questionnaire in full were not included in the study even though they met the inclusion criteria.

Measures

The study, carried out with 85 participants who agreed to participate in the study and met the inclusion criteria, was implemented in two phases when the data were collected: February 1-28, 2020, and November 1-30, 2020.

Participants' socio-demographic characteristics were collected by face-to-face interview method.

Pain

Pain of the cases were assessed with Visual Analog Scale (VAS). VAS is a 0-10 cm (or 0-100 mm) horizontal line denoting the absence of pain at one end and the most severe pain at the other end (27). VAS has advantages since it is easy to understand and apply and it has been found reliable and valid in studies to measure the severity of menstrual pain (28).

Menstrual Symptoms

The cases' menstrual symptoms were determined with Menstruation Symptom Questionnaire (MSQ). This scale was developed by Chesney and Tasto in 1975 to evaluate menstrual

pain and symptoms, and a Turkish validity and reliability study was conducted by Güvenç et al. in 2014. The five-point Likert type scale consists of 22 items and 3 sub-dimensions: "Negative effects/somatic complaints", "Menstrual pain symptoms" and "Coping methods" (29, 30).

Physical Activity Levels

Participants' physical activity levels were evaluated by International Physical Activity Questionnaire (IPAQ), developed by Craig et al. (31). The validity and reliability study of the questionnaire was conducted by Sağlam in Turkey in 2010 (32). This study utilized the self-report short IPAQ form "last 7 day recall" to evaluate the level of physical activity for the last seven days. In this study, individuals were divided into 3 groups as physically inactive (<600 MET-minutes/week), with insufficient physical activity (600-3000 MET-minutes/week) and with adequate physical activity level (>3000 MET-minutes/week) (33).

Statistical analysis

The data obtained in the study were analyzed with the Statistical Package for the Social Sciences (SPSS) Program version 25.0 (New York, IBM Corp) by writing the minimum, maximum, mean and standard deviation values for numerical values. The data were normally distributed according to the Kolmogorov-Smirnov test. Therefore the parametric tests were used for statistical analyses. The related-sample t-test was used to determine the difference between first and second assessment. A p value of <0.05 was considered statistically significant.

Ethics

Before starting the study, ethics committee approval was obtained from the Scientific Research and Publication Ethics Committee of Cappadocia University (Decision no: 2020.22-Application no: 29533901-204.07.07-11321). After the participants were informed about the content of the study, they read and signed the informed consent form stating that they voluntarily participated in the study. This study was conducted in accordance with the Declaration of Helsinki.

RESULTS

The cases mean age (min:19- max:27) was 20.75±1.23 years old. The body mass index (BMI) of the individuals participating in this study was determined to be 21.50 ± 3.36 kg/m² (n=85) before the pandemic and 21.97 ± 3.15 kg/m² (n=85) during the pandemic. While the severity of dysmenorrhea of participants was 6.23 ± 1.78 (n=85) before the pandemic, it was 7.20 ± 1.63 (n=85) during the pandemic. While the individuals' total MSQ score was 6.23 ± 1.78 (n=85) before the pandemic, it was 7.20 ± 1.63 (n=85) during the pandemic. It was found that the participants' IPAQ score was 1274.67 ± 1232.26 (n=85) before the pandemic, it was 902.74± 892.33 (n=85) during the pandemic (Table 1). Based on physical activity levels, individuals were divided into 3 groups as physically inactive, not active enough and active. It was observed that 60% (n=51) of the participants were in the "not active enough" group before the pandemic, and 55.3% (n=47) were in the "inactive" group during the pandemic (Table 1).

Table 1. Participants' Age and BMI, VAS, MSQ, IPAQ Scores Before and During the Pandemic

			Minimum (n: 85)	Maksimum (n: 85)	Mean ± SD (n: 85)
Age			19	27	20.75 ± 1.23
BMI (kg/m²)		1. assessment	16.9	29.4	21.50 ± 3.36
		2. assessment	16.7	32.8	21.97 ± 3.15
VAS		1. assessment	2	10	6.23 ± 1.78
		2. assessment	3	10	7.20 ± 1.63
MSQ		1. assessment	41	96	74.01 ± 13.09
		2. assessment	49	105	79.00 ± 13.88
IPAQ		1. assessment	66	8226	1274.67 ± 1232.26
		2. assessment	66	4590	902.74 ± 892.33
			%	n	
Physical Activity Levels	Inactive	1. assessment	31.8	27	
	Not active enough		60	51	
	Active		8.2	7	
	Inactive	2. assessment	55.3	47	
	Not active enough		42.4	36	
	Active		2.3	2	

*BMI: Body mass index, VAS: Vizüel Analog Scale, MSQ: Menstruation Symptom Questionarre, IPAQ-SF: International Physical Activity Questionnaire.

There was a statistically significant difference between the mean scores of cases' VAS (t= -3.549, p=0.001) and IPAQ (t= 2.543, p=0.013) before and during the pandemic. There was no statistically significant difference between the mean MSQ (t= -0.781, p=0.437) and BMI (t= -,938, p=0.351) scores of cases before and during the pandemic (Table 2).

Table 2. Participants' VAS, MSQ and IPAQ Scores Before and During the Pandemic

		n	Mean ± SD	t	p
VAS	1. assessment	85	6.23 ± 1.78	-3.549	0.001
	2. assessment	85	7.20 ± 1.63		
MSQ	1. assessment	85	74.01±13.09	-.781	0.437
	2. assessment	85	79.00±13.88		
IPAQ	1. assessment	85	1274.67 ± 1232.26	2.543	0.013
	2. assessment	85	902.74 ± 892.33		
BMI	1. assessment	85	21.50 ± 3.36	-.938	0.351
	2. assessment	85	21,97 ± 3,15		

VAS: Vizüel Analog Scale, MSQ: Menstruation Symptom Questionarre, IPAQ: International Physical Activity Questionnaire, BMI: Body Mass Index.

DISCUSSION

In the study in which we investigated the effect of physical inactivity on dysmenorrhea, changes were detected in physical activity level, pain and menstrual symptom scale. The most important findings of this study was the decrease in the physical activity during pandemic period and increase in pain due to dysmenorrhea. In addition although the MSQ score and BMI score changed negatively during the pandemic, it did not show a statistically significant change. In their study, Gurel et al. (2021) examined the change in body mass during the lockdown period in the COVID-19 pandemic and reported that 44.6% (n=116) of the participants had an increase in body weight (34). In a different study conducted with women with dysmenorrhea, mean BMI was found to be 21.63±2.98 kg/m² (n=23) (35).

It was determined that the difference between the 1st and 2nd BMI scores of the cases was approximately 0.50 kg/m². According to BMI, the results of the study show parallelism with the literature.

Takeda et al. (2021) reported that the VAS value increased when compared to the pre-pandemic measurements, and this increase was statistically significant (36). Buran and Öter (2022) reported that menstrual pain was more severe in those who had COVID-19 and this pain change was statistically significant (37). In this study, it was reported that the VAS values of the participants, which show the severity of dysmenorrhea, increased during the pandemic compared to the pre-pandemic period (p=0.001). According to VAS, the result of the study shows parallelism with the literature. The increase in the pain intensity of the participants may be due to the decrease in their physical activity levels.

It has also been reported that the increase in body mass index causes edema in the extremities, cramps, back pain and an increase in the severity of dysmenorrhea (38, 39). It can be thought that the decrease in physical activity levels and increase in BMI in the pandemic period may be among the factors provoking pain.

The increased number of MSQ scores reflected that negative situations in menstrual symptoms. In their study Issa et al. (2022) found prepandemic score is 70.04 ± 18.02, pandemic score is 72.65 ± 21.72 (40). They examined the change MSQ score was significantly found after the pandemic compared to before it. According to the results of our study changing in MSQ scores from 74.01±13.09 to 79.00±13.88 were found. Although there was differences between the score of assesments, this chancing scores was not statistically significant.

CONCLUSION

This study, which examined the effect of physical inactivity/ sedentary lifestyles on dysmenorrhea, concluded that the pandemic conditions decreased participants' physical activity levels and increased their VAS and BMI values. Hence, increasing the level of physical activity can reduce the negative effect of dysmenorrhea, which seriously affects the quality of life. In order to minimize the negative impact of the pandemic on physical activity, quality time can be spent by following exercise programs from media communication tools during the time spent at home. Physical activities such as walking, running, climbing and ascending-descending stairs can be done in open areas.

LIMITATIONS

The limited age range of the sample and hence the assessment of individuals in similar age ranges along with the probability that the MSQ score may change if the individuals are not in the same menstrual period are the limitations of this study.

Author Contribution: Study Design - DTA, AY; Design – DTA, AY, GB; Data Search - DTA, AY, GB, BB, OB, SV; Statistical Analysis – BB, OB; Literature Review - DTA, AY, GB; Data Interpretation - DTA, AY, GB; Critical Review - BB, OB; Manuscript Preparation- DTA,AY; Literature- DTA, AY, GB. All authors have read and agreed to the published version of the manuscript.

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Nurses' Experiences While Opening a Pediatric Intensive Care Unit: A Qualitative Study

Hemşirelerin Çocuk Yoğun Bakım Kurma Deneyimi: Nitel Çalışma Örneği

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Abstract

Background and purpose: This qualitative research was conducted to explore the experiences of nurses while opening a new intensive care unit.

Methods: The semi-structured interviews were conducted with nine nurses working in the pediatric intensive care unit at Muğla Education and Research Hospital. This pediatric intensive care unit is a new unit that opened on October 19, 2020.

Results: The results of the research consist of the nine nurses' experience while opening the Pediatric Intensive Care Unit (PICU). The nurses stated that they lacked supplies and equipment in the first days of the PICU that the situation resulted in a loss of manpower. The nurses stated that they were afraid and worried about medical errors and pediatric care because they had no experience in caring for children. All nurses were assigned to different departments due to low patient numbers in the first few months. It was found that the nurses felt anxiety and their motivation decreased because they did not know what kind of work environment they would find in this PICU and which patients they would care for.

Conclusion: It is recommended to plan the number of staff for the unit according to the number of beds, and to employ these nurse professionals in the field of pediatric units before the PICU.

Keywords: Experience, pediatric intensive care, pediatric nurse

Özet

Çalışmanın Konusu ve Amacı: Bu nitel araştırma, yeni bir yoğun bakım ünitesi kuran hemşirelerin bu süreçte yaşadıkları deneyimlerini incelemek amacıyla yapılmıştır.

Yöntem: Muğla Eğitim ve Araştırma Hastanesi Çocuk Yoğun Bakım Ünitesi 19 Ekim 2020 tarihinde kurulan yeni bir ünitedir. Araştırmada Muğla Eğitim ve Araştırma Hastanesi Çocuk Yoğun Bakım Ünitesinde kurulma aşamasından itibaren çalışan dokuz hemşire ile yarı yapılandırılmış görüşmeler gerçekleştirilmiştir.

Bulgular: Araştırma bulgularını yoğun bakım deneyimi olan dokuz hemşirenin yoğun bakım kurma sürecinde yaşadıkları sorunlar oluşturmaktadır. Hemşireler yoğun bakım kurulma sürecinin ilk günlerinde malzeme ve cihaz yetersizliği yaşadıklarını ve durumun iş gücü kaybına neden olduğunu belirtmişlerdir. Çocuk hastanın bakımında deneyimli olmadıkları için hemşireler tıbbi hata ve pediatrik bakım konusunda korku ve endişe yaşadıklarını ifade etmişlerdir. Hemşirelerin tamamı ilk aylarda hasta sayısının az olması nedeniyle farklı birimlerde görevlendirilmiştir. Bu birimlerde nasıl bir çalışma ortamı ile karşılaşacaklarını ve hangi hastalara bakım vereceklerini bilmedikleri için hemşirelerin anksiyete yaşadıkları ve motivasyonlarının azaldığı belirlenmiştir.

Sonuç: Yaşanacak sorunların önüne geçmek için; hastane idaresi ile iş birliği sağlanarak medikal malzemelerin erken temin edilmesi, yatak sayısına uygun olarak birimde çalışacak görevli sayısının planlanması ve bu sağlık profesyonellerinin kendi birimleri kurulana kadar pediatri alanında istihdamının sağlanması önerilmektedir.

Anahtar Kelimeler: Çocuk yoğun bakım, pediatri hemşiresi, deneyim

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INTRODUCTION

Intensive care units are departments that care for patients with one or more organ failures, who require intensive care after trauma, and where many procedures are performed. Due to the use of advanced technological equipment in intensive care units, it is important for the care and treatment of patients that the medical professionals who work in these units are knowledgeable, experienced, and qualified (1).

The intensive care units are divided according to their specialties. Depending on the diagnosis and care needs, pediatric patients are cared for in the Pediatric Intensive Care Unit (PICU) and the Neonatal Intensive Care Unit. The PICUs are units where children aged one month to 18 years whose medical condition is critical are admitted, closely followed, and monitored, advanced life support is provided and multidisciplinary care and treatment are provided (2). This units are designed differently than those for adults. The principles of family-centered care are applied in these units. This units are organized so that the child's parents or legal guardians can stay with the child for 24 hours, as long as the unit and the patient's condition permit (3).

When a tracheotomy was performed in 1950 on a Danish child with respiratory distress due to polio, the lack of PICUs became apparent. The first PICU was established in Sweden in 1955, followed by Europe, Australia, and North America after 1960. In our country, the first PICU was opened at Istanbul College Medical School in 1994 (2). Half of the PICUs in our country became operational in the early 2000s. The criteria for admission to a second- and third-level unit are also different. Children diagnosed with respiratory failure, cardiac arhythmias, fluid-electrolyte imbalance, epilepsy, diabetic ketoacidosis, and gastrointestinal bleeding are admitted to a second-level pediatric intensive care unit, while third-level units admit more severe patients such as chronic renal failure, organ transplantation, cardiac disease disrupting hemodynamics, head trauma, and spinal cord injury (4).

Nurses, who are an integral part of the health care system, have an important position in the delivery of health care services (5). Especially in intensive care units, the nurse is the most important member of the care team, as he or she is primarily responsible for the care of the patient (6). Intensive care nurses are the team members who spend a long time with the patient in the units, notice the slightest change and treat, care for and, if necessary, perform the first intervention on the patient. Critical care nurses should possess the qualities of critical thinking, rapid clinical decision making, use of medical equipment, and harmonious collaboration, as well as their knowledge and skills related to applied care. These qualities they are expected to possess, along with critical patient care, can increase the anxiety level of nurses working in intensive care units (7). In addition to the heavy workload, pediatric nurses working in the intensive care unit also experience the emotionality of caring for a critical child, the problems of the family and the child, and the intense process of loss. In addition, the simultaneous care of children at different stages of development may require them to demonstrate different communication skills. For example, it may be difficult for pediatric nurses to care for a one-month-old baby and a 16-year-old adolescent at the same time (8). Therefore, there is a need for highly skilled nurses in PICUs.

The main responsibilities of pediatric critical care nurses are: Prevent infections, assess the patient using scores and scales used in intensive care units, monitor the patient, provide close care, plan and apply appropriate nursing care, perform the patient's breathing exercises and provide appropriate care to the patient connected to the ventilator, perform procedures such as suctioning, positioning, and postural drainage. This also includes providing appropriate nursing care to reduce pressure ulcers and risk factors, providing and applying oral, enteral, and parenteral nutrition to the patient, and assisting the patient and family in obtaining psychosocial support and resources (1,2,7,9).

Improving the quality of care in intensive care units and managing critical patients is possible with the options available to the healthcare team. Proper planning of the unit design, adequately qualified medical staff, and well-functioning supplies and equipment are important requirements for these units. The intensive care units must be properly planned to increase the quality of work and reduce workload. The provision of adequate medical equipment, regular calibration of instruments, appropriate placement of materials, proper planning of lighting and ventilation systems directly contribute to the care provided by the healthcare team working in intensive care units (10).

Nurses play an active role in planning, providing materials, and creating a work order in a newly opened intensive care unit. For this reason, no research on this topic was found during the literature search. It is expected that the experiences of nurses while opening a new unit will contribute to the healthcare team going through the same process. This qualitative research was conducted to examine nurses' experiences during the opening of the 3rd level pediatric intensive care unit, which opened on October 19, 2020, in a 500-bed training and research hospital.

METHODS

This qualitative study was conducted to explore the experiences of nurses while opening a new pediatric intensive care unit.

Research Questions:

What are the experiences of nurses while opening a PICU?

What are the factors that influence nurses' experiences?

What are the suggestions for experiences while opening the PICU?

Setting

The pediatric intensive care unit at Muğla Education and Research Hospital was opened on October 19, 2020. During the opening of the unit, nine nurses and one physician worked. In this study, semi-structured interviews are conducted with nine nurses working in this PICU of Muğla Education and Research Hospital. The research data was collected using a semi-structured interview form consisting of four questions prepared based on the literature, and expert opinions were obtained. The questions were related to four themes describing the experience of setting up the PICU (unfamiliarity with the child patient, lack of supplies/equipment, transfer to other units as a supplementary nurse, adjustment/orientation problems).

Data collection

The purposive sampling method used to identify participants resulted in the selection of nine nurses working in the PICU at Muğla Education and Research Hospital. Purposive sampling method consists of individuals who can provide appropriate responses for the purpose of the study (11). Purposive sampling allows for an in-depth study of situations that are thought to be rich in information (12).

In qualitative studies, small groups are generally preferred. This is because in large groups, observation and interviewing begin to be repetitive at a certain point and cause additional time to be spent. In qualitative studies, the data should be detailed rather than broad (12,13).

Table 1: Personal Characteristics of Participants

Participants	Age	Gender	Years of work	Experience in Intensive Care Unit	Experience with Pediatric Patients	Voluntary Transition
Nurse E1.	26	F	4	Yes	No	No
Nurse E2.	32	F	10	No	Yes	Yes
Nurse Ç.	34	F	12	Yes	Yes	Yes
Nurse G.	27	F	4	Yes	Yes	Yes
Nurse B.	43	M	13	Yes	No	Yes
Nurse Ş.	32	F	10	Yes	No	Yes
Nurse R.	40	F	19	Yes	Yes	Yes
Nurse S.	30	M	7	Yes	No	Yes
Nurse K.	26	K	4	Yes	Yes	Yes

It can be seen that the personal characteristics of the nurses who participated in the study were similar (Table 1).

Ethical consideration

Prior to the study, approval was obtained from the Ethics Committee of Muğla Sıtkı Koçman University of Health Sciences (Decision Number: 81-Decision Date: 26.04.2021), approval was obtained from the Muğla Provincial Health Directorate, and informed consent was obtained from the nurses participating in the study.

External and internal validity and reliability of the study

The study paid attention to the concepts of external and internal validity and reliability. To ensure the internal validity of the study, expert opinions and consent of the nurses participating in the study were obtained for the interview questionnaire used in the study before its use. To ensure the external validity of the study, the period of implementation of the study is given, the process of data analysis and the selection of methods used in the study are explained. To ensure the internal reliability of the study, data loss was prevented by using a recording device, and the results were shared without comment. To ensure the external reliability of the study, the consistency of the results was checked.

Statistical analysis

The data collected in qualitative research is analyzed in two ways: descriptive and content analysis (14). The data obtained from this research was analyzed using the 'Descriptive Analysis' method.

- A framework was created to group the obtained data.
- The data were analyzed using the created framework.
- The processed data were defined and some data were directly evidenced by the nurses' sentences.
- The results were explained and interpreted.

RESULTS

The study interviewed nine nurses about the process of being placed in a newly opened unit and their experiences during this time. Four frames (themes) were formed when examining the responses and this frame was supported by the nurses' sentences.

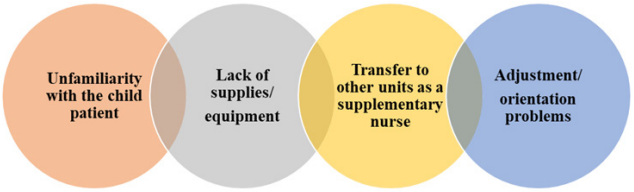

Figure 1. Structured Interview Themes

Theme 1. Unfamiliarity with the child patient

Since nurses have not yet been assigned according to the specialty nursing staff, they may be assigned to adult or pediatric patients depending on the decision of the hospital administration, the needs of the unit, and the demand for

nurses. Since a pediatric intensive care unit was opened for the first time in the hospital where the study was conducted, the nurses working in this unit were transferred from other departments of the hospital, especially pediatric services. For this reason, it was found that team members, generally composed of nurses providing health services to adult patients, experienced anxiety and hesitation when caring for pediatric patients who were in critical condition. The statements of the three nurses who participated in the research on this topic were as follows:

"I did not feel competent, I started very hesitantly because I did not have any experience with children." (Nurse E1.)

"I was very excited in the PICU, I wanted to volunteer, I had never seen a pediatric patient before, I was most afraid of the dose calculation of the medications." (Nurse S.)

"I have always worked in the adult units, I wanted to transfer because I thought the pediatric patient would be less stressful, but since I had never worked before, I was nervous in case I could not make it." (Nurse G.)

Theme 2. Lack of supplies/equipment

One of the most important components of care and treatment in the intensive care unit is the medical equipment and special devices. When planning the opening of the unit, purchase and supply requests for special materials and equipment were made. However, the delivery time for some equipment has been extended, and some equipment and materials could not be obtained for reasons beyond our control. The lack or limitation of these materials and equipment not only makes patient care more difficult, but also decreases the motivation of nurses working in the department and leads to loss of manpower. Nurses' opinions on this issue are as follows:

"The biggest challenge we faced was the lack of equipment. We did not even have a pumping device. We did not have a nebulizer, we started with a big shortage. So we had a lot of difficulties." (Nurse C.)

"Our materials are very inadequate. Our equipment was inadequate." (Nurse E1.)

"There were shortages of materials, but it is still not quite finished. Because we continue to have difficulties in working." (Nurse E2.)

"We had material problems in the first month because it is a newly opened department." (Nurse K.)

"The lack of some special and important materials gave us a hard time. We were looking for supplies and equipment from other units." (Nurse R.)

Theme 3. Transfer to other units as a supplementary nurse

In newly opened departments, patient acceptance is initially low. However, staff scheduling is done as if the unit is at full capacity, even though the number of patients is low according to current written regulations. This PICU was also fully staffed, but when the number of patients was low, the nurses working there were assigned to other units by hospital managers during working hours. It was found that reasons such as the lack of continuity of the additional assignments, the change in working hours, and the lack of notification to the staff during work scheduling led to psychological pressure and loss of motivation among the staff. Nurses' statements on this issue are as follows:

"Managers would send us to other departments and say, 'You have a patient or two.' In fact, I was pulled off to another department during my first shift. I think we could have taught each other more if we had been here at the time. But we struggled for a long time because we were not in PICU." (Nurse E2.)

"Of course, there were departures in the opening phase because there were not enough patients to begin with. Nurses were pulled to other areas. Then, of course, as the number of patients increased, we continued to work in our place." (Nurse K.)

"Our first shift was a bit of a nuisance because we were moved to other units because of the small number of patients." (Nurse R.)

"Since we have a small number of patients, we were reassigned to other departments in the hospital." (Nurse B.)

"On my first shift there was a 40-day-old baby who was admitted to the hospital with suspected internal bleeding, the baby had to be hungry. He was crying for 24 hours and I could not move because my colleagues were pulled off to other departments. It was the worst shift in my life." (Nurse S.)

Theme 4. Adjustment/orientation problems

It was found that the nurses who started working in the unit had difficulty adapting to the PICU because they had no experience in caring for pediatric patients and were constantly assigned to other wards. The nurses who had difficulty adjusting commented on this issue as follows:

"If we had been trained on the equipment here, we might have been able to adjust more easily if they had tried to train us here, if they had not pulled us to other units during our first shifts." (Nurse E2.)

"If our materials had been fully obtained and opened, the adjustment would have been easier, that process would have gone better if we had not been pulled off to other units." (Nurse S.)

DISCUSSION

Most of the nurses interviewed have critical care experience and volunteered to join the team to work in the newly opened pediatric intensive care unit. The fact that the nurses choose the ward where they will work contributes to their positive

thoughts and high motivation. In the study by Yeşiltaş and Gül (2016), it was found that the job satisfaction of nurses who choose the unit they will work in is high (15). Although most of the nurses participating in the study have experience in intensive care units where adult patients are located, they do not have experience caring for pediatric patients. Although the nurses volunteered to prefer the newly opened PICU, they indicated that they experienced fear and anxiety when caring for pediatric patients. It is well known that pediatric patients are not miniature adults and have different care needs. Children receiving care in the pediatric intensive care unit are vulnerable and depend on nurses to meet their needs. Pediatric nurses can assess children's care needs holistically, with a care plan developed in accordance with the principles of atraumatic and family-centered care (16,17). In Mattsson et al.'s (2013) qualitative study of nurses' concerns in PICU, it was found that nursing care was not always responsive to the child's needs and compromised the child's well-being (18).

Nurses participating in the study stated that caring for a pediatric patient requires more attention and they are afraid of making medical and medication errors. Because pediatric doses are calculated individually based on the patient's age, body weight, body surface area, and clinical condition, the administration dose of each medication varies. In addition, medication errors are more likely to have serious and fatal consequences in pediatric patients than in adults (19,20).

The nurses participating in the study stated that they were assigned to different services due to the low number of patients in this newly opened department and that this rotation schedule had a negative effect on them. In the study by Durmuş et al. (2018), it can be seen that there is a significant difference between the constant rotation of the department, the way of working and the duration of overtime and the burnout scores of the nurses (21). In this study, it was found that nurses had difficulty keeping up with the operation of their assigned departments and that this situation caused them anxiety. It was found that caring for adult patients on some workdays and caring for pediatric patients on some workdays resulted in role conflict.

The medical equipment and materials to be used in this newly opened PICU were executed in accordance with the appropriate procedures. When the pediatric patients were admitted to the ICU, the lack of equipment and supplies and the lack of training in the use of equipment led to a loss of motivation among nurses and a loss of manpower. According to the study by Karayurt et al. (2018), it was found that nurses spend 30% of their time searching for materials and equipment, resulting in loss of motivation (22). According to the study of Koç et al. (2017), it was found that the inability of nurses to find appropriate equipment increases the stressful situation at work (23).

Limitations

The limitation of this study is the fairly small sample size of PICU nurses.

CONCLUSION

During the opening of the PICU, nurses expressed their experiences under the headings of unfamiliarity with the pediatric patient, lack of supplies/equipment, transfer to other departments as an additional nurse, and adjustment/orientation problems. In the absence of comparable research in the literature, it is anticipated that this qualitative study will contribute to the understanding of the emotions experienced by health professionals when opening a new department. To prevent the problems that may occur, it is recommended to work with the hospital managers to provide early medical care, plan the number of staff for the unit according to the number of beds, and employ these health professionals in pediatric units before the PICU.

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Comparison Of Walking Parameters In Adolescent Idiopathic Scoliosis And Healthy Adolescents

Sağlıklı ve İdiyopatik Skolyozu Adölesanlarda Yürüme Parametrelerinin Karşılaştırılması

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Abstract

Aim: This study was planned to evaluate gait differences in healthy adolescents with adolescent idiopathic scoliosis (AIS). In addition, it was aimed to evaluate the correlation between gait parameters and other variables of patients with AIS.

Material-Method: Forty adolescent individuals were included in the study. While 20 of these individuals were patients with AIS, 20 were healthy adolescents. In this study, gait analysis of each case was evaluated with Biodex Unweighing System (Inc. Shirley, USA), spinal deformity perceptions with Walter Reed Visual Assessment Scale (WRVAS), self-perception of trunk deformity with Trunk Appearance Perception Scale (TAPS) , quality of life with Scoliosis Research Society-22 (SRS-22), and fear of movement was assessed with the Tampa Scale of Kinesiophobia (TSK).

Result: According to the results of our study; Compared to the healthy control group, subjects with AIS have been shown to differ significantly, they had shorter duration of standing on one leg (p=0.028), shorter mean stride cycle (p=0.003), longer mean right stride length (p= 0.035), longer mean left stride length (p=0.039) and worse ambulation indices (p=0.036). In addition, statistically significant correlations were found between Cobb angle and WRVAS and TAPS in the group with AIS, and between walking speed and age, One Leg Standing Time, TSK and stride cycle (p<0.05).

Conclusion: As a result, it was determined that some gait parameters of patients with AIS showed deviations from normal when compared to healthy adolescents.

Keywords: Adolescent idiopathic scoliosis, gait parameters, Quality of life , Kinesiophobia, Scoliosis Perception.

Özet

Amaç: Bu çalışma adölesan idiyopatik skolyozlu (AİS) sağlıklı adölesanlarda yürüyüş farklılıklarını değerlendirmek için planlanmıştır. Ayrıca AİS'li hastaların yürüyüş parametreleri ile diğer değişkenler arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya 40 adölesan birey dahil edildi. Bu bireylerin 20'si AİS'li hasta iken, 20'si sağlıklı adölesanlardan oluşmaktadır. Bu çalışmada her bireyin yürüme analizi Biodex Unweighing System (Inc. Shirley, ABD), spinal deformite algıları Walter Reed Görsel Değerlendirme Skalası (WRVAS) ile, gövde deformitesinin benlik algısı Trunk Appearance Perception Scale (TAPS) ile yaşam kalitesi Skolyoz Araştırma Derneği-22 (SRS-22) ile ve hareket korkusu Tampa Kinezyofobi Ölçeği (TSK) ile değerlendirildi.

Bulgular: Çalışmamızın sonuçlarına göre; Sağlıklı kontrol grubu ile karşılaştırıldığında, AİS'li bireylerin anlamlı farklılık gösterdiği, tek ayak üzerinde durma sürelerinin daha kısa (p=0,028), ortalama adım döngülerinin daha kısa (p=0,003), ortalama sağ adım uzunluklarının daha uzun olduğu (p= 0.035) ve daha uzun ortalama sol adım uzunluğu ile (p=0.039) daha kötü ambulasyon indeksleri (p=0.036) olduğu gösterilmiştir. Ayrıca AIS'li grupta Cobb açısı ile WRVAS ve TAPS arasında ve yürüme hızı ile yaş, tek ayak üzerinde durma süresi, TSK ve uzun adım döngüsü arasında istatistiksel olarak anlamlı korelasyonlar bulundu (p<0,05).

Sonuç: Sonuç olarak AİS'li hastaların bazı yürüme parametrelerinin sağlıklı adölesanlara göre normalden sapmalar gösterdiği belirlendi.

Anahtar Kelimeler: Adölesan idiyopatik skolyoz, Yürüme parametreleri, Yaşam kalitesi, Kinezyofobi, Skolyoz Algısı.

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INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a progressive growth condition characterized by a three-dimensional deformation of the spine with lateral curvature and rotation of the vertebral bodies (1). It is the most prevalent form of pediatric scoliosis and the most common type of orthopedic disorder (2). People between the ages of 10 and 16 are most often affected during the growth spurt just before puberty. The incidence of AIS is estimated to be between 1% and 3% of the population, Female are more vulnerable than male (3).

The most common human movement in daily activities is walking. There are several advantages to walking properly with the proper technique and posture. It can help you avoid back problems and muscular pains, lower your chance of injury, and much more. It's not difficult to walk with the proper gait and posture, but it does require some practice. However, in AIS it's important to know the effectiveness of spine deformation on gait parameters (walking speed, step cycle, step length, time on each foot, and ambulation index result), AIS has been shown in several studies to alter the connective structure of the spine, resulting in changes in mobility and balance. Previous studies varied in terms of Gait patterns it's differed between patients with AIS and their healthy peers in some studies (4, 5, 6, 7, 8, 9, 10). On the other hand, Lao et al. (11) did not find a significant difference in ambulation index between the two groups or between the right and left limbs. In addition, spatiotemporal gait parameters did not differ significantly between the two groups, according to Schmid et al (12). It did not show significant differences between the two groups. These contradictory results in most of the previous studies that were conducted might be due to variable differences in assessing asymmetries, which requires more studies to determine the origin and consequences of these results. The existing data on AIS is minimal, and the majority of the data comes from a limited body of research.

INDIVIDUALS AND METHODS

40 individuals aged 10-18 years were evaluated after getting the agreement of the patient's carers. Applied in Ahi Evran University, School of Physical Therapy and Rehabilitation Kırşehir, Turkey. The study was conducted between September 2021 and December 2021. The study was approved by the Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. 20 AIS patients in our study demonstrated varying severity of spinal deformity from mild, less than 20 degrees, to even more than 45 degrees of Cobb's angle according to Lenke criteria. In addition 20 age-matched peers without idiopathic scoliosis, exercise therapy contraindicated, previous surgical intervention for scoliosis, and individuals with other disorders were excluded from the study.

At the beginning, the demographic data of the subjects (age, gender, height, weight, dominant side, and term birth) was evaluated face-to-face. We utilize a scoliometer to assess Cobb angle in addition to the clinical type (scoliosis type, severity, assistive devices, and orthoses). Furthermore, we described their perception of spine deformity by using the Walter Reed Visual Assessment Scale (WRVAS), Trunk appearance perception scale (TAPS) for assessing self-perception of trunk deformity, the Scoliosis Research Society (SRS-22) Scoliosis Patient Questionnaire for assessing QOL and psychological well-being, and the Tampa scale of kinesiophobia (TSK) A Scoliosis Patient Questionnaire to assess their feelings or intuitions about what is happening with their body and a one-leg stance time test to determine postural stability in a static position. Last, Gait assessment analysis with Biodex Unweighting system for calculating gait parameters and motion analysis. We utilized Biodex Unweighting system for collecting measurements of gait parameters (walking speed, step cycle, step length, time on each foot, and ambulation index result), with these differences of variables we could measure asymmetry ratio of gait parameters. Each subject in this study barefoot naturally walked almost a certain distance at a comfortable pace.

SPSS v.25.0 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis. Normal distribution was evaluated by Kolmogrov-Smirnov and Shapiro-Wilk tests. The groups were compared with the Independent t test, and the $p<0.05$ value was considered statistically significant.

RESULTS

Twenty (6 boys, 14 girls) with AIS and 20 (6 boys, 14 girls) healthy adolescents were included in the study. The mean Cobb angle values of the patients with scoliosis included in the study were determined as 22.35± 21.1 degrees. The socio-demographic characteristics of the cases are shown in Table 1.

Table1. Socio-demographic characteristics of individuals

			minimum	maximum	X±SS	p
AGE(year)		AIS	11th	18	15.65 ± 2.03	0.505
		NORMAL	14	18	16.00 ± 1.12	
BMI (kg / m²)		AIS	15.5	34.3	21.03 ± 4.95	0.546
		NORMAL	15.6	28.3	21.84 ± 3.20	
SRS		AIS	71	99	84.05 ± 8.43	-
TSK		AIS	27	43	34.90 ± 6.39	-
WRVAS		AIS	7	42	13.70 ± 7.35	-
TAPS		AIS	3	10	5.70 ± 2.27	-
			n	%	p*	
GENDER	AIS (n=20)	male	6	30.0	1,000	
		female	14	70.0		
	NORMAL (n=20)	male	6	30.0		
		female	14	70.0		
DOMINANT SIDE	AIS (n=20)	RIGHT	15	75.0	0.072	
		LEFT	5	25.0		
	NORMAL (n=20)	RIGHT	19	95.0		
		LEFT	1	5.0		

BMI: Body mass index, cm: centimeters, kg: kilograms, kg/m2: kilograms/ meter2, X±SD: mean±standard deviation. SRS-22: Scoliosis Research Society Quality of Life Questionnaire-22, TSK: Tampa Scale of Kinesiophobia Patient Questionnaire,

WRVAS: Walter Reed Visual Assessment Scale, TAPS: Trunk Appearance Perception Scale, *p<0.05 Chi-square test, p<0 .05 independent samples t-test.

It was determined that there was no musculoskeletal problem in the history and family history examination of the cases. In order to determine the negative effect of hand predisposition on gait asymmetry, the dominant side was additionally investigated in all patients participating in the study. While there were 15 right dominant individuals in AIS cases, 19 right dominant individuals were identified in the healthy group. In addition, it is seen that there is no difference between the two groups in terms of gender and dominant side (p<0.05). (Table 1).

Table 2. Comparison of walking parameters of individuals participating in the study

	GROUP	X ± SD	t	p*
ONE LEG STANDING TEST (SN)	AIS	3.09 ± 2.96	-2.28	0.028
	CONTROL	5.19 ± 2.86		
AVERAGE WALKING SPEED	AIS	0.787 ± 0.127	-1,719	0.094
	CONTROL	0.84 ± 0.079		
AVERAGE STEP CYCLE	AIS	0.35 ± 0.223	-3,219	0.003
	CONTROL	0.54 ± 0.162		
AVERAGE STEP LENGTH-RIGHT	AIS	0.73 ± 0.084	2,185	0.035
	CONTROL	0.67 ± 0.086		
AVERAGE STEP LENGTH-LEFT	AIS	0.68 ± 0.106	2,142	0.039
	CONTROL	0.61 ± 0.095		
TIME ON RIGHT FOOT	AIS	61.35 ± 12.35	1,324	0.193
	CONTROL	56.35 ± 11.52		
TIME ON LEFT FOOT	AIS	38.65 ± 12.35	-1,024	0.092
	CONTROL	43.65 ± 11.52		
AMBULATION INDEX	AIS	49.05 ± 21.85	-2,177	0.036
	CONTROL	62.70 ± 17.56		

AIS: Adolescent Idiopathic Scoliosis, **X±SS**: mean±standard deviation, p<0.05 independent sample t-test.

The mean age of individuals with AIS was 15.65 ± 2.03 years, and the control group was 16.00 ± 1.12 years. (t =0.674; p > 0.05). In addition, there was no statistically significant difference in BMI between the AIS and control groups included in the study. (t =0.61; p > 0.05) (Table 1).

When the cases were compared with each other in terms of dominance, there was no statistically significant difference between the two groups (t = 1.83; p= 0.072) (Table 1).

There was no statistically significant difference between the AIS group and the control group in terms of mean walking speed (t = 1.71) (p > 0.05). However, there was a statistically significant difference between the groups in terms of the mean step cycle. On the other hand, the mean right stride length showed a statistically significant difference when the AIS group and the control group were compared (t = 2.18; p=0.035). In addition, there is a statistically significant relationship between the two groups in the mean left stride length. (t = 2.14; p = 0.039) (Table 2).

There was no statistically significant difference between the groups in the time on each foot (right t = 1.324; p = 0.193, left t = -1.024; p = 0.092) (Table 2). A statistically significant difference was found between the AIS group and the control group in terms of ambulation index (t = -2.177; p= 0.036) (Table 2).

The results of the correlation analysis performed in the group with AIS are shown in chart 1,2,3. A positive and significant relationship was found between the patients' AWS values and ASC, TSK, OLST,

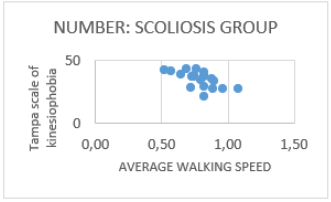

chart.1

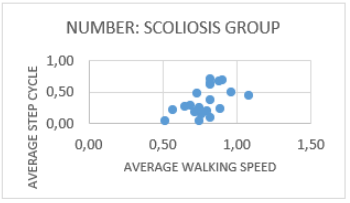

chart.2

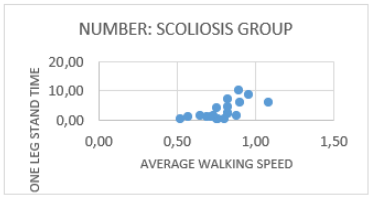

chart.3

DISCUSSION

According to the results of this study, it was shown that there were significant differences in some variables, shorter OLST, shorter mean stride cycle, longer mean right stride length, longer mean left stride length and worse ambulation indices in patients with AIS compared to the healthy control group. In addition, statistically signif icant correlations were found between Cobb angle and WRVAS and TAPS in the group with AIS, and between AWS and age, OLST, TSK and ASC. However, no statistically significant correlation was found between Cobb angle and any gait parameters in patients with AIS.

We evaluated postural balance with the one-leg standing test to see if AIS patients had poor postural balance compared to a healthy same-aged control group. AIS patients have a shorter one-leg standing test suggesting that they have poorer postural balance. Overall, our findings were consistent with findings from multiple previous studies that showed differences in postural balance between AIS and healthy controls (13, 14). In other studies, it was reported that there was no difference in postural balance between AIS and healthy controls (15-16). A direct comparison between studies is difficult, as various research procedures and consequently various outcome measures are used. It needs static balance in activities where many tasks such as walking are effective. Differences in research results can be attributed to differences in age and/or curve characteristics of the population studied. In individuals with AIS curvature of the spine creates an imbalance in upper body postural alignment, which can compromise postural balance. However, currently available research on balance in AIS patients is inconsistent. In this study, it was determined that there were differences in mean stride cycle, right stride length, left stride length and

ambulation index in patients with AIS compared to healthy controls in terms of gait parameters. In addition, no statistically significant difference was found between the right and left sides in terms of mean walking speed and time on each foot in our study. Haber et al (9) reported a decrease in the mean walking speed of the patients in their study evaluating the walking of patients with scoliosis. In contrast, Yang et al. (5) found that the AIS group did not differ from the control group in all spatio-temporal variables. However, according to Chen et al., stance phase, cadence, stride length, and angular movement of the lower limbs of normal participants were also similar to those of AIS participants (7). the findings show that more comprehensive studies are needed to clearly determine the effects of the scoliotic spine on lower extremity mechanics. Park et al. (17) claimed that by reducing these variables, the intra-phase coordination in the transverse plane of the thoracic-pelvis coordination pattern increased. This is one example of how individuals with AIS have a less steady gait than healthy people. According to Mahaudens et al., in individuals with severe scoliosis, the stride length and stance phase period are shortened and further reduced over time (4). Reduced cadence, Giakas et al. (18). According to Kramers-de Quervain et al. asymmetry in trunk movement is an explanation of low walking speed in patients with scoliosis (19). Other studies think that this decrease is due to impaired balance control in AIS cases (20). The aim of this study was to see if AIS patients had worse ambulation compared to a healthy control group of the same age. The results showed that the AIS group had a weaker ambulation index. These inconsistent results might be owing to the degree of the participants' spinal deformities varying between researches. We believe that the discrepancies are attributable to variances in the degree of spinal deformity, the position of the curvature in the spine, and the control of postural stability of the body center for AIS patients across studies.

The mean Cobb angle of the patients with AIS included in our study was 22 degrees. All of these cases consisted of cases with Lenke Type 1 curvature. However, since these cases were compared with their healthy peers, some gait differences were detected. The mean stride length on both sides was found to be less in the AIS group than their healthy peers. This may also have caused changes in mobility and balance. Our results showed that there is a significant relationship between mean walking speed and mean stride cycle in AIS. This means that as the velocity decreases, the stance phase of the cases increases and the swing phase duration decreases. The swing/stance measure ratio is a valuable clinical measure for detecting gait asymmetries. Chan et al. (11) supports the lack of significant differences in the swing/stance ratios of scoliotic and non-scoliotic subjects compared to normal subjects. Mahaudens et al (4) found that the stance phase was significantly shortened in all scoliosis groups.

Our findings revealed that there was no correlation between Cobb angle and all gait parameters in the cohort of AIS patients in this study, suggesting that ambulation was not affected by the severity of the disease. This is in line with Mahaundens et al. (4) who found that scoliosis severity was not associated with changes in gait parameters in the AIS. Syczewska et al. (21) found that scoliosis severity and type of pelvic deformity affected walking speed, cadence, and stride length. Scoliosis grade affected gait pathology in all kinematic parameters. The degree of spinal malformation and pelvic tilt are associated with gait parameters (22, 23). Asymmetry in gait and the degree of the curve are related (24). These conflicting findings differ from the number of participants.

In addition, statistically significant correlations were found between Cobb angle and WRVAS and TAPS in the group with AIS in our study. Pineda et al. (25) state that WRVAS and scoliosis severity are related. They diagnosed individuals with a mean age of 19.4 years of idiopathic scoliosis, and the mean sizes of the thoracic curve and the lumbar curve were 36.6° and 33.2°, respectively. Their findings showed that participants were not aware of very mild curvatures. Percentages indicate that the test will show high sensitivity to changes that occur as scoliosis worsens; An improvement following the correction of the deformity is perceived only in severe deformities.

Our study showed that there is a significant relationship between TSK and mean walking speed in AIS ($p = 0.004$). No significant correlation was found with other walking parameters. Our findings consistent with the results of Haddas et al. (26) they reported that the TSK score showed a high correlation with walking speed, stride, double support times, and stride length, and a moderate correlation with cadence and stride length. Although walking speed was measured to see how it affected walking, each participant in this study naturally walked a specified distance, barefoot at a comfortable pace on a Biodex Weightless System (Inc., Shirley, USA). Due to this comfortable self-paced structure in our results, there was no significant difference in mean walking speed between the AIS and the control group may be the reason. Patel et al. walking slowly will help you focus more on complex cognitive activities that will improve your performance while walking (27). As a result of the significant correlation between TSK and mean walking speed, this means that in AIS cases the fear of walking fast increases and it may affect other walking parameters, leading to an asymmetrical gait. In conclusion, in the light of the data obtained from this study, fear of movement in AIS cases has been a subject that has been frequently emphasized in recent years, and TSK stands out among the factors affecting gait parameters that cause asymmetrical cases. In these cases, it is thought that the increased walking speed in AIS restricts the feelings and intuitions about what is happening in your body, therefore it is thought that such

individuals may limit their physical functions. Our results also showed that there is a highly significant relationship between TSK and the one-leg standing test. In light of these data, it is a difficult task to increase walking speed while keeping the center of mass within the safety limits of the base of support so as not to lose balance. Thus, a significant correlation could mean that there is a weakness in balance and is affected by feelings or intuitions about what is happening in your body, and balance is affected by gait speed, so more balance means less fear of movement and therefore better gait in AIS. In this regard.

These conflicting findings may be due to the number of participants (only 20 AIS in our study), the fact that we included only Lenke type 1 participants or that our study was conducted on a moderate scoliotic curve (mean Cobb angle = 22). Thus, this seems to relatively weaken the role of hump prominence or trunk balance in associated pain in AIS cases. This can be interpreted as why quality of life is not correlated with Cobb angle or scoliosis shape. This is in line with the findings of the study conducted by Asher et al. (28) In a study conducted in a case study, no relationship was found between the type of curve and quality of life.

This study was conducted on healthy adolescents and AIS living in Kırşehir. We measured the gait parameters of the subjects and found a significant or clinically significant asymmetry between the left and right sides. In conclusion, our study shows that AIS individuals have gait asymmetries in some biomechanical parameters. Moreover, it is clear that more research is needed on AIS cases with larger case groups and various curve shapes and ages. On the other hand, the findings of the study are important in terms of allowing comparison of guiding results for future research on this subject.

CONCLUSION

1- We conducted conventional gait parameters research in our study and our results showed a significant difference in mean stride cycle and both foot stride length results between the AIS group and the healthy control group.

2- It was determined that the ambulation index obtained from the Biodex Weightless System of the patients with AIS was significantly lower than the healthy control group. In this case, we can say that there are deviations from normal in the gait of patients with AIS.

3- Contrary to expectations, no relationship was found with Cobb angle in patients with AIS. Considering that the Cobb angles of the subjects included in the study were 22 degrees on average, we think that it is unlikely to be related to gait parameters.

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The Role Of Dietary Polyphenols In The Regulation Of Cell Life Signaling Pathways

Hücre Yaşamı İle İlgili Sinyal Yolakların Düzenlenmesinde Diyet Polifenollerin Rolü

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Abstract

This study investigated the modulatory impact of dietary polyphenols in the regulation of some signaling pathways related to cell life. The study included mammalian target of rapamycin (mTOR), phosphatidylinositol-3-kinase (PI3K)/AKT, nuclear factor-kappa β (NF-κB), mitogen-activated protein kinase (MAPK) and Wnt/β-catenin signaling pathways. In addition, dietary polyphenols of curcumin, quercetin, apigenin, resveratrol, gallic acid are included. Relevant signaling pathways or dietary polyphenols were identified as keywords. These keywords were searched in scientific databases such as PubMed, Institute for Scientific Information Web of Science, Google Scholar, Scopus and Science Direct. 48 sources were examined, especially considering the research in the last ten years. In conclusion, it emerges as a new approach in the treatment and prevention of diseases with the regulatory effect of dietary polyphenols in the regulation of multiple cell signaling pathways such as NF-κB, MAPK, Wnt/β-catenin and PI3K/AKT/mTOR. Natural polyphenols, which can suppress the molecular and cellular pathways associated with inflammation, have the potential to be used in the treatment and prevention of chronic inflammatory illnesses. Therefore, understanding the mechanistic actions involved in modulating these signaling pathways by dietary polyphenols will provide useful information for the development of future functional foods for disease treatment and prevention.

Keywords: NF-kB; MAPK; Wnt/β-catenin; PI3K/AKT/mTOR; curcumin; quercetin; apigenin; resveratrol; gallic acid.

Özet

Bu çalışma, hücre yaşamı ile ilgili bazı sinyal yolakların düzenlenmesinde diyet polifenollerin modülatör etkisini değerlendirmeye almıştır. Çalışmaya mammalian target of rapamycin, fosfatidilinositol-3-kinaz (PI3K)/AKT, (mTOR), nükleer faktör-kappa β (NF-κB), mitojenle aktive olan protein kinaz (MAPK) ve Wnt/β-katenin sinyal yolakları dahil edilmiştir. Buna ek olarak kurkumin, kuersetin, apigenin, resveratrol, gallik asit diyet polifenolleri dahil edilmiştir. İlgili sinyal yolakları veya diyet polifenolleri anahtar kelime olarak belirlenmiştir. Bu anahtar kelimeler PubMed, Institute for Scientific Information Web of Science, Google Scholar, Scopus ve Science Direct gibi bilimsel veri tabanlarında taranmıştır. Özellikle son on yıl yapılan çalışmalar dikkate alınarak 48 referans incelenmiştir. Sonuç olarak, MAPK, NF-κB, PI3K/AKT/mTOR ve Wnt/β-katenin gibi çoklu hücre sinyal yolakların düzenlenmesinde diyet polifenollerinin modülatör etkisi, hastalıkların önlenmesi ve tedavisinde yeni bir yaklaşım olarak ortaya çıkmaktadır. Enflamasyonla ilişkili moleküler ve hücresel yolları baskılayabilen doğal polifenoller, kronik inflamatuar bozuklukların önlenmesinde ve tedavisinde kullanılma potansiyeline sahiptir. Bu nedenle, diyet polifenolleri tarafından bu sinyal yolaklarının modüle edilmesinde yer alan mekanik eylemlerin anlaşılması, hastalıkların önlenmesi ve tedavisi için gelecekteki fonksiyonel gıdaların geliştirilmesi için yararlı bilgiler sağlayacaktır.

Anahtar kelimeler: NF-kB; MAPK; Wnt/β-catenin; PI3K/AKT/mTOR; kurkumin; kuersetin; apigenin; resveratrol; gallik asit.

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1. GİRİŞ

Hayatta kalma sinyali, hücre ölüm mekanizmasını bastırmak ve sinir sistemindeki apoptotik sinyali dengelemek için çok önemlidir (1). Çok çeşitli hücre sinyal yolları ve bunların etkileşimleri, iskemi, beyin travması, gelişimsel bozukluklar ve yaşa bağlı nörodejenerasyon ile ilişkili nöroenflamasyonda hayati roller oynar. Nöronların yanı sıra mikroglia ve astrositler de proinflamatuar sitokinler, kemokinler ve reaktif oksijen türleri salarak inflamatuar kaskadı etkiler. Nöral disfonksiyona yanıt olarak proinflamatuar mediatörlerin salınması, normal hücresel hayatta kalmaya yardımcı, nötr ve hatta zararlı olabilir (2).

Kardiyovasküler hastalıklar dahil olmak üzere birçok fizyolojik süreçte merkezi bir rol oynayan ve aynı zamanda çeşitli proliferatif sinyalleri, besin ve enerji bolluğunu ve stresli durumları entegre eden mammalian target of rapamycin (mTOR) sinyal yolağı, yaşlanma ile ilişkili kronik stres, mitokondriyal disfonksiyon ve düzensiz otofaji arasında merkezi düzenleyici olarak görev yapar (3). Ayrıca, mTOR sinyal yolağının da dahil olduğu çoklu hücre sinyal yollarında ki anormallikler, çok adımlı bir süreç olan karsinogenezde önemli rol oynamaktadır (4). Buna ek olarak, mitojenle aktive olan protein kinaz (MAPK) sinyal yolağındaki anormallikler de, karsinogenez sürecine önemli bir katkıda bulunur ve bu nedenle, hücre farklılaşması, proliferasyon, istila, anjiyogenez, apoptoz ve metastaz dahil olmak üzere karsinogenezin çeşitli yönlerinde rol oynar. Bu yol, antikanser aktivite için modüle edilebilen ve birkaç malignite için büyük ilgi gören çoklu moleküler hedefler sunar (5). Bu sinyal yolaklarında ki anormallikleri düzenlemek, karsinogenez sürecini tersine çevirmede etkili olabilir (4).

Polifenoller, gıda kaynaklarında bol miktarda bulunan önemli bir fitokimyasal gruptur (6). Fenolik bileşikler açısından zengin gıdaların tüketiminin çeşitli hastalık riskini azaltabileceği defalarca gösterilmiştir (7,8). Polifenollerin nörodejeneratif hastalıklarda, hipertansiyon ve diğer kardiyovasküler hastalıklarda, kanserde, inflamasyonda, diyabette, dislipidemide, alerjide ve bağışıklık sistemi hastalıklarında terapötik değere sahip olduğu bildirilmiştir. Ayrıca karaciğer, prostat, ve kolorektal kanserden lenfoblastik lösemiye kadar farklı kanser türlerinin önlenmesinde rolleri olduğu bildirilmiştir (9). Ayrıca polifenollerin güçlü antioksidan özelliğini doğrulamıştır ve vitamin E ve C'den daha etkili olabildiğini göstermiştir (10). Biyolojik bir sistemdeki polifenollerin antioksidan aktivitesinin esas olarak redoks özelliklerinden, şelatlama yeteneklerinden ve elektronları transfer etme kapasitelerinden kaynaklandığı öne sürülmüştür (11).

Son araştırmalar, polifenollerin nükleer faktör-kappa β (NF-κB), Wnt/β-katenin, fosfatidilinositol 3-kinaz ve protein kinaz B (PI3K/AKT) ve MAPK sinyal yolaklarını modüle edebildiğini göstermiştir (12). Birçok rapor, diyet polifenollerinin ve metabolitlerinin, anti-enflamatuar aktivitelerini sadece antioksidan kapasiteye değil, aynı zamanda önemli hücresel fonksiyonları oynayan hücre içi sinyal yollarının çeşitli bileşenleri üzerindeki seçici eylemler yoluyla hücrelerdeki modüle edici aktiviteye de uyguladıklarını göstermektedir (13).

Bu çalışma, hücre yaşamı ile ilgili bazı sinyal yolaklarınının (PI3K/AKT/mTOR, MAPK, NF-κB ve Wnt/β-katenin) düzenlenmesinde diyet polifenollerin modülatör etkisi üzerine tasarlanmıştır. Özellikle son on yılda yayınlanan ilgili çalışmalar, PubMed, Institute for Scientific Information Web of Science, Google Scholar, Scopus ve Science Direct gibi bilimsel veri tabanlarından seçilmiştir. İlgili çalışmaları bulmak için kullanılan anahtar kelimeler sinyal yolakları (PI3K/AKT/mTOR, MAPK, NF-κB ve Wnt/β-katenin) veya polifenollerdi.

2. SİNYAL YOLAKLARI

2.1. PI3K/AKT ve mTOR sinyal yolakları

PI3K/AKT/mTOR sinyal yolağı , hücre döngüsünü düzenlemede elzem olan bir hücre içi sinyal yoludur. Hücresel durgunluk, çoğalma, kanser ve uzun ömür ile doğrudan ilişkilidir. PI3K aktivasyonu AKT'yi fosforile eder ve aktive ederek onu plazma zarında lokalize eder (14). Birçok kanserde bu yol aşırı aktiftir, bu nedenle apoptozu azaltır ve proliferasyona izin verir. Tümör hücresi hayatta kalması ve hücre proliferasyonu, PI3K/AKT/mTOR hiperaktivasyonu , tümör baskılayıcı gen p53 ve glikolitik enzim Laktat dehidrogenaz A'nın inaktivasyonundan kaynaklanır. PI3K/AKT/mTOR sinyal yolağının aşağı regülasyonu, apoptozu indükler ve hücre sağkalımını durdururken, AKT/protein kinaz B ve serin/treonin kinaz, PI3K'nın (apoptozu bloke eden temel kinaz) en önde gelen aşağı akış efektörleridir (12). Bununla birlikte, bu yol, yetişkin kök hücrelerin, özellikle nöral kök hücrelerin farklılaşması üzerinde büyümeyi ve çoğalmayı teşvik etmek için gereklidir (15). Ek olarak, bu yolun nöral uzun vadeli güçlenmede gerekli bir bileşen olduğu bulunmuştur (16). PI3K/Akt/mTOR sinyal yolağı, tüm sporadik insan kanserlerinde en sık hedeflenen yollardan biridir. Reseptör tirozin kinazlar veya Ras tarafından tetiklenen aktive edilmiş PI3K, birkaç hücre içi ağ molekülünü harekete geçirir ve en çok tercih edilen aşağı akış hedefi AKT'dır (17). PI3K/AKT/mTOR sinyal yolağına ait olan mTOR, stresli durumları entegre eden serin/treonine özgü bir protein kinazdır (3).

2.2. MAPK sinyal yolu

MAPK sinyal yolu, hücre yüzeyinde yer lan bir reseptörden gelen bir sinyali, hücrenin çekirdeğinde yer alan DNA'ya

ileten hücredeki bir protein zinciridir. Sinyal yolu, bir sinyal molekülünün hücre yüzeyinde yer alan reseptöre bağlanmasıyla başlar. Bu bağlanma sonucu çekirdekte yer alan DNA, bir proteinin oluşumuna yol açtığında ve hücrede bazı değişiklikler (hücre bölünmesi gibi) ürettiğinde sona erer. Yolak, orijinal olarak hücre dışı sinyalle düzenlenen kinazlar (ERK'ler) olarak adlandırılan, komşu bir proteinin fosforile olması (fosfat grupları eklenmesi) ile iletişim kuran ve böylece bir "açık" veya "kapalı" anahtar gibi davranan mitojenle etkinleştirilen protein kinazlar (MAPK'ler) gibi birçok proteini içerir. Yolakdaki proteinlerden biri mutasyona uğradığında, onun kanser gelişiminde bir rolü olabilir. Mutasyon sonucunda oluşan protein "açık" veya "kapalı" konumda takılmakta ve bu durumda farklı hücresel sinyallere cevap vermemektedir. Bu duruma göre, anormal aktiviteye neden olan bu proteine bağlanarak çoğalma ortaya çıkarabilecek hücrelerin sayisi artacaktadir. Aslında, MAPK sinyal yolağının bileşenleri ilk olarak kanser hücrelerinde keşfedildi ve "açma" veya "kapama" anahtarını tersine çeviren ilaçlar, kanser tedavisi olarak araştırılmaktadır (18).

MAPK'ler, hücre dışı uyaranları gen ekspresyonu, apoptoz, hayatta kalma, mitoz, proliferasyon, farklılaşma, enflamatuar tepkiler ve hücresel stres dahil olmak üzere çok sayıda hücresel aktiviteye dönüştürmede bir odak noktası görevi gören protein kinazların yüksek oranda korunmuş üyeleridir . Oksidatif stres, büyüme faktörleri, enflamatuar sitokinler, DNA hasarı ve ısı şoku gibi çeşitli hücre dışı uyaranlarla uyarılırlar (19). MAPK/ERK sinyal iletim yolağı, hücre büyümesine, hayatta kalmasına, hareketliliğine ve farklılaşmasına katkıda bulunan ana faktör olarak hizmet eder. ERK'nın, anti-apoptotik protein Bcl-2'yi yukarı doğru düzenleyerek, cAMP yanıt element bağlayıcı proteini (CREB) aktive ederek ve Bcl-Xl/Bcl-2 bağlantılı ölüm promotörünü inhibe ederek hayatta kalma yanlısı sinyallemeye aracılık ettiği yaygın olarak bilinir (20).

2.3. NF-κB sinyal yolu

NF-κB, sitokin üretimini, DNA transkripsiyonunu ve hücre sağkalımını kontrolünde yer alan bir protein kompleksidir. NF-κB genel itibariyle tüm hayvan hücre türlerinde bulunur ve sitokinler, stres, ağır metaller, serbest radikaller, okside düşük dansiteli lipoprotein (LDL), ultraviyole ışınlama ve viral veya bakteriyel antijenler gibi uyaranlara verilen hücresel tepkilerde yer alır (21). NF-κB, enfeksiyona ilgili bağışıklık sisteminin düzenlenmesinde hayati derecede önemli bir rol oynar. NF-κB'nin yanlış düzenlenmesi enflamatuar hastalıklar, otoimmün hastalıklar, kanser, viral enfeksiyon, septik şok, ve uygun olmayan bağışıklık gelişimi ile ilişkilendirilmiştir. NF-κB, sinaptik plastisite ve hafıza süreçlerinde de yer almıştır (22). NF-κB sinyal yolağında, siklooksigenaz-2'nin (COX-2) ekspresyonu ve tümör nekroz faktör-ą, interlökin-8, ve interlökin-6 gibi proinflamatuar sitokinlerin sentezi düzenlenir. Normal bir hücrede, sitoplazmik NF-κB proteinleri, NF-κB inhibitörü ile bağlanır ve sitoplazmada inaktif durumda kalır (23). Aktif durumda olan NF-κB proteinleri sitoplazmadan çekirdeğe yer değiştirir ve çeşitli enflamatuar hastalıklara yol açan hedef gen aktivasyonuna aracılık eder (24).

2.4. Wnt/β-katenin sinyal yolu

Wnt/β-katenin sinyal yolu, sinyalleri hücre yüzeyi reseptörleri yoluyla bir hücreye ileten proteinlerle başlayan bir sinyal iletim yolları grubudur . Wnt adı, Wingless ve Int-1 adlarından oluşturulmuştur. Bu sinyal yolağı, ya yakındaki hücre-hücre iletişimini (parakrin) ya da aynı hücre iletişimini (otokrin) kullanır. Hayvanlarda yüksek oranda evrimsel olarak korunurlar, bu da meyve sineklerinden insanlara kadar hayvan türlerinde benzer oldukları anlamına gelir (25). Wnt/β-katenin sinyal yolağı, hücre göçü, doku yapısı, organ oluşumu ve hücre proliferasyonunu düzenlemedeki temel rolleriyle tanınmaktadır . Artrit, kanser, retinopati ve tetra-amelia dahil olmak üzere birçok hastalık, bu sinyal ağının düzensizliği ile bağlantılı olabilir (26). Kanonik Wnt sinyal kaskadında, β-katenin olarak bilinen bütünleyici bir protein, merkezi bir bileşen görevi görür. β-Katenin, Wnt proteinlerinin görünmemesinde kazein kinaz 1 ve glikojen sentaz gibi çok yönlü bir proteinler tarafından fosforile edilir. Fosforile edilmiş β-katenin, bir ubikuitin-proteomal bozunma sistemi tarafından parçalanır. Bu nedenle, çekirdekteki hedef genler tetiklenmez. Wnt glikoproteinlerinin kıvrımlı reseptöre bağlanması, sitoplazmada dağınık proteinin aktivasyonunu destekler. Bu aktivasyon, β-katenin fosforilasyon aktivitesinin azalmasına ve müteakip bozulmasına neden olur. β-katenin'in sitoplazmada biriken bu stabil formu, hücre çekirdeğine yer değiştirir ve Wnt hedef genlerinin ortaya çıkmasına aracılık etmek için T-hücresi faktörü/lenfoid transkripsiyon arttırıcı faktöre bağlanır (27).

3. DİYET POLİFENOLLERİ

Kurkumin, kuersetin, apigenin, resveratrol, ve gallik asit gibi bazı diyet polifenollerinin anti-enflamatuar ve antikanser aktiviteleri, iltihaplanma ile ilişkili çeşitli hücre sinyal iletim yolları, yani NF-κB, MAPK, PI3K/AKT/mTOR ve Wnt/β-katenin sinyal yolaklari üzerindeki modülatör etkilerinden kaynaklanmaktadır (12).

3.1. Kurkumin

Birkaç zerdeçal türünün rizomlarından izole edilen kurkumin, bir α,β-doymamış karbonil bazlı polifenoldür. Çeşitli hayvan toksisite çalışmaları ve sağlıklı gönüllüler üzerinde yapılan klinik deneyler, kurkuminin yüksek dozlarda bile güvenli olduğunu göstermiştir. Zerdeçal, gastrointestinal sistem yoluyla zayıf emilimi nedeniyle düşük biyoyararlanıma sahiptir, bu nedenle önemli farmakolojik etkiler elde etmek için yüksek dozlara ihtiyaç vardır (28).

Kurkumin, farmakolojik aktivitelere ve çeşitli sinyal olaylarını modülatör etkisi bulunmaktadır (29).

Akut monositik lösemi SHI-1 hücrelerinin kurkumin ile tedavi edilen apoptozunu değerlendirmek için bir in vivo araştırma yürütmüştür . İlginç bir şekilde, MAPK fosforilasyonu, kurkumin tedavisinden sonra aktive olurken, NF-κB ve ERK1 ve ERK2'nin fosforilasyonu bastırıldığı tespit edilmiştir (30). Başka bir çalışmada, kurkumin tedavisinin, MCF-7 meme kanserinde p44/42 MAPK fosforilasyonunu aşağı doğru düzenlediği bildirilmiştir. Araştırma, kurkuminin büyümeyi baskıladığı ve MAPK sinyal yolağı yoluyla hücrelerin kaspazla tetiklenen apoptozisini harekete geçirdiği sonucuna varmıştır (31). Zerdeçal aracılı meme karsinojenez modülasyonunun antikanser aktivitesinin, esas olarak MAPK, NF-κB, Wnt/β-katenin, PI3K/AKT/mTOR ve JAK2/STAT3 sinyal ağları üzerindeki aktivitesine bağlı olduğu da bildirilmiştir (32).

3.2. Kuersetin

Kuersetin, en çok elma, turunçgiller, kırmızı soğan, böğürtlen, kiraz, brokoli, kişniş, kapari gibi sebze, meyve ve çay besin kaynaklarında bulunur (33). Kuersetinin, JNK MAPK yolağını tetiklemenin yanı sıra hücre sağkalımı için zorunlu olan ERK MAPK dahil olmak üzere birçok sinyal proteinini baskılayarak HepG2 hücrelerinin büyümesini azalttığı saptanmıştır (34). Başka bir çalışmada, kuersetin (50 μM), NF-κB transkripsiyon faktörünü inaktive ederek ve AP-1/JNK sinyal yolunu tetikleyerek HepG2 hücre ölümü üzerinde in vitro kemopreventif etkiler sergilediği belirtilmiştir (35). A375A insan melanom hücreleri üzerinde çeşitli konsantrasyonlarda (3.1 ila 50 μM) kuersetin tedavisi, sinyal ileten proteinler ile birlikte siklin D1, β-katenin ve COX-2 dahil olmak üzere aşağı akış hedef genlerinin karşılanmasını önleyerek Wnt/β-katenin ağının modülasyonunu kolaylaştırmıştır (36).

3.3. Apigenin

Apigenin, birçok doğal glikozidin bir aglikonudur ve kimyasal olarak 4',5,7-trihidroksiflavon olarak bilinir. Kereviz, kişniş, papatya , maydanoz, biberiye, soğan, çay ve portakal gibi çok sayıda meyve ve sebzenin önemli bir bileşenidir (37).

Apigenin biyolojik ve farmakolojik aktiviteleri, anti-enflamatuar, antioksidan, antikanser, anti-proliferatif ve anti-spazmodik dahil olmak üzere çeşitlidir. Apigenin'in osteosarkom hücreleri, prostat kanseri, mesane kanseri hücreleri, karaciğer kanseri ve kolorektal kanser hücreleri dahil olmak üzere çeşitli kanser hücre dizilerine karşı sitotoksik etkileri iyi araştırılmıştır. Apigenin, sinyal yollarını değiştirerek apoptoz üzerinde güçlü bir inhibisyon sergilemiştir. Ancak altta yatan mekanizmaların daha fazla açıklığa kavuşturulması gerekmektedir (12). Apigenin, MAPK ve PI3K/AKT/mTOR sinyal ağlarını modüle ederek koriokarsinom hücrelerinin ilerlemesini ve metastazını önleyerek önemli kemopreventif özellikler sergilemiştir (38). Apigenin'in, Wnt/β-katenin sinyalini etkisiz hale getirerek kolorektal kanser hücrelerinin ilerlemesini engellediği saptanmıştır. Apigenin ayrıca birikmiş β-katenin'in çekirdeğe girişini de bastırdığı, bu da daha sonra Wnt sinyali ile bağlantılı akış aşağı moleküllerin baskılanmasıyla sonuçlandığı belirtilmiştir (39). Başka bir çalışma, apigenin konsantrasyonuna bağlı olarak β-katenin aşağı regülasyonuna aracılık ederek Wnt/β-katenin sinyalini inhibe ettiğini göstermiştir. Sonuçlar, apigenin konsantrasyonu 10 μM'den yüksek olduğunda %60'tan fazla inhibisyon oluştuğunu göstermiştir. Bu, Wnt ile ilgili yaşamı tehdit eden hastalıklar için potansiyel bir tedavi olabilir (40). Apigenin kronik rinosinüzitte MAPK ve NF-κB sinyal yolağını en aza indirerek nazal mukozanın yeniden şekillenmesini azaltmıştır (41).

3.4. Resveratrol

Resveratrol, flavonoid olmayan bir polifenol ve fitoaleksin ve stilbenin türevidir . Dut, yaban mersini, ahududu, kırmızı şarap, yer fıstığı ve üzüm gibi çeşitli diyet ürünlerinde ve bitkilerde bulunur (42). Resveratrol'ün çeşitli farmakolojik ve biyolojik aktiviteler sergilediği ve çeşitli sinyal yollarını modüle ettiği bildirilmiştir (33). Diyabetik farelerle yapılan bir çalışma, resveratrolün diyabet aracılı kardiyak disfonksiyonu iyileştirdiği ve etkilerin, kalpte MAPK ve ERK sinyal yolaklarının inflamatuvar mediyatörlerinin azalması ve zayıflaması ile birlikte olduğunu ortaya koymuştur (43). Resveratrol'ün, p38 MAPK/NF-κB yolunu önemli ölçüde aşağı doğru düzenlediği gösterilmiştir (44). Resveratrol, hücrelerde p-PI3K ve p-AKT ekspresyonunu inhibe ederek hücre döngüsü ilerlemesini bastırmıştır. Bu bulgular, hücre döngüsünün durdurulduğunu göstermiştir. İnsan mide kanserindeki MGC803 hücrelerinin sayısı, PI3K/AKT sinyal yolaklarının düzenlenmesi yoluyla resveratrol tarafından indüklenmiştir (45).

3.5. Gallik Asit

Kimyasal olarak 3,4,5-trihidroksibenzoik asit olarak adlandırılan gallik asit, genellikle çay yapraklarında, mazıda, cadı fındığında, sumakta, meşe kabuğunda ve diğer bitkilerde bulunur (46). Gallik asit, insan glioma hücrelerinde hücre proliferasyonu, invazyonu ve hayatta kalmasıyla ilgili Ras/MAPK ve PI3K/AKT sinyal yolaklarının fosforilasyonunu aşağı doğru düzenlediği bildirilmiştir (47). Ho ve arkadaşları (2013), gallik asidin (3,5 μM) NF-κB aktivitesini inhibe ettiğini ve AKT/small'ı aşağı regüle ettiğini göstermiştir. Bu sonuçlara dayanarak, gallik asit, mide kanserini tedavi etmek için bir antikanser ajan olarak geliştirilme potansiyeline sahiptir (48).

4 . SONUÇ

MAPK, PI3K/AKT/mTOR, NF-κB ve Wnt/β-katenin gibi çoklu hücre sinyal yolakların düzenlenmesinde diyet polifenollerinin modülatör etkisi ile hastalıkların önlenmesi ve tedavisinde yeni bir yaklaşım olarak ortaya çıkmaktadır. Enflamasyonla ilişkili moleküler ve hücresel yolları baskılayabilen doğal polifenoller, kronik inflamatuar bozuklukların önlenmesinde ve tedavisinde

kullanılma potansiyeline sahiptir. Bu nedenle, diyet polifenolleri tarafından bu sinyal yolaklarının modüle edilmesinde yer alan mekanik eylemlerin anlaşılması, hastalıkların önlenmesi ve tedavisi için gelecekteki fonksiyonel gıdaların geliştirilmesi için yararlı bilgiler sağlayacaktır.

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