



**TURKISH
JOURNAL OF
HEALTH
AND
SPORT**



**TURKISH JOURNAL OF
HEALTH AND SPORT**

E-ISSN 2757-5446

**TJHS 2021, Vol. 2, Issue 3
TURKEY**

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The Oxidative Stress and Antioxidants in Scientific Research

Bilimsel Arařtırmalarda Oksidatif Stres ve Antioksidanlar

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Received: 30/10/2021

Accepted: 26/11/2021

Published Online: 02/12/2021

Abstract

Oxidative stress, which is caused by the effect of many factors in living organisms, must be constantly balanced by the antioxidant system. The continuous formation of free oxygen radicals for many reasons, especially aerobic respiration, increases oxidative stress. The antioxidant system is formed by various enzymes, vitamins and many other structures. All these antioxidant structures are constantly working to neutralize oxidative stress products and to establish a balance. In order to maintain the oxidant-antioxidant balance, lifestyle changes such as healthy and balanced nutrition and increasing mobility are of great importance in living organisms. Today, oxidative stress and antioxidants are frequently measured both in various experimental models established in experimental animals and in clinical studies, which is becoming increasingly important. For this reason, oxidant-antioxidant balance indicator parameters are very valuable in scientific research. In addition, newly established different in vivo models have started to measure oxidative stress and antioxidant status. For this reason, our internationally indexed journal TJHS will give priority to scientific research on oxidant-antioxidant balance and publish current scientific developments in this field.

Keywords: Oxidative status, antioxidant status, oxidative stress, antioxidant activity.

Özet

Canlı organizmalarda birçok faktörün etkisi ile oluşan oksidatif stres sürekli biçimde antioksidan sistemce dengelenmelidir. Oksijenli solunum başta olmak üzere birçok sebeple sürekli olarak serbest oksijen radikallerinin oluşumu oksidatif stresi artırır. Antioksidan sistem çeşitli enzimler, vitaminler ve bunların dışındaki birçok yapı tarafından oluşturulur. Bütün bu antioksidan özellikli yapılar, sürekli olarak oksidatif stres ürünlerini etkisiz hale getirmek ve bir denge kurmak için çalışmaktadırlar. Oksidan-antioksidan dengesinin korunması için, canlı organizmalarda, sağlıklı ve dengeli beslenilmesi, hareketliliğin artırılması gibi yaşam tarzı değişikliklerinin büyük önemi bulunmaktadır. Günümüzde giderek önemini arttıran biçimde, hem deney hayvanlarında kurulan çeşitli deneysel modellerde hem de klinik çalışmalarda oksidatif stres ve antioksidanlar sıklıkla ölçülmektedir. Bu sebeple oksidan-antioksidan denge göstergesi parametreler bilimsel arařtırmalarda çok değerlidir. Ayrıca yeni kurulan farklı invivo modeller de oksidatif stres ve antioksidan durumu ölçmeye başlamıştır. Bu sebeple uluslararası alan indeksli dergimiz TJHS, oksidan-antioksidan denge ölçülen bilimsel arařtırmalara öncelik verecek ve bu alandaki güncel bilimsel gelişmeleri yayınlayacaktır.

Anahtar kelimeler: Oksidan durum, antioksidan durum, oksidatif stres, antioksidan aktivite.

Cite this article: Savas HB, Kara E. The Oxidative Stress and Antioxidants in Scientific Research. Turk J Health S. 2021;2(3):pp.28-30.



Introduction

Oxidative stress, which is caused by the effect of many factors in living organisms, must be constantly balanced by the antioxidant system (1-5). The continuous formation of free oxygen radicals for many reasons, especially aerobic respiration, increases oxidative stress. The antioxidant system is formed by various enzymes, vitamins and many other structures. Although superoxide dismutase, catalase, glutathione peroxidase, glutathione S transferase, paraoxonase 1, arylesterase, glutathione, vitamins A, C and E are the main antioxidants, there are many antioxidant structures apart from these (6-10). All these antioxidant structures are constantly working to neutralize oxidative stress products and to establish a balance. In order to maintain the oxidant-antioxidant balance, lifestyle changes such as healthy and balanced nutrition and increasing mobility are of great importance in living organisms. If the balance in question is disturbed due to reasons such as weakening of the antioxidant system or excessive increase in oxidative stress, oxidative damage begins in cells, tissues and organs (11-15). Oxidative damage gradually damages many structures, especially the cell membrane, organelle membrane, nucleus membrane, genetic material. It disrupts protein, carbohydrate and lipid structures. As the oxidative damage that starts in this way accumulates and increases, physiological processes such as aging are accelerated, and hundreds of multifactorial fatal diseases such as cancer, cardiovascular diseases and diabetes mellitus are triggered (16-20). For this reason, the measurement and evaluation of oxidative stress and antioxidants is a current and important issue in health-related scientific research. The number of experimental and in vivo studies in this field is increasing day by day (21-22).

As the number of studies increases, novel research methods are also developing. Due to the fact that the oxidant and antioxidant system is formed by many components, some of these components were tried to be measured separately. In the second stage, the idea was carried out by measuring oxidative stress products such as protein carbonyl, malon dialdehyde, which are formed by oxidative damage. Finally, parameters such as total oxidant status, total antioxidant status and oxidative stress index have been developed to show the general status of the antioxidant and oxidant system. However, new generation parameters such as native thiol, total thiol and calculated thiol-disulfide balance, ischemia modified albumin have begun to be measured frequently (17-18).

Thiols are also known as mercaptans. Thiols are organic compounds containing compounds of hydrogen and sulfur atoms attached to a carbon atom. The plasma thiol pool contains mainly albumin thiols, protein thiols, low molecular weight thiols. Thiols can undergo oxidation reactions via oxidants and form disulfide bonds. Disulfide bond is a covalent

bond and is also called SS bond or disulfide bridge. Under oxidative stress, cysteine residues alternately form disulfide bonds between protein thiol groups and low molecular weight thiols. Native thiol and total thiol measurement dynamically displays thiol balance. The disulfide bonds can be reduced back to thiol groups, thus maintaining the dynamic thiol disulfide equilibrium (17-18).

Paraoxonase 1 and arylesterase antioxidant and enzymes that work for vascular health are used to determine ischemic lesions and to show antioxidant status. LDL oxidation accelerates atherosclerosis. Inflammation and oxidative stress lead to oxidation of LDL. The release of monocyte chemoattractant protein-1 from endothelial cells will lead to the migration of monocytes. These phagocytize oxidized LDL (oxLDL) into foam cells. PON1 hydrolyzes oxLDL. oxLDL converts back to LDL. Thus, PON1 inhibits the progression of atherosclerosis. It contributes to the cholesterol balance and the prevention of oxidation and ensures the protection of vascular health (20-21).

In addition to health sciences, there are various studies to investigate the balance of oxidative stress-antioxidant capacity in sports sciences (22). Examination of antioxidant capacity in sports sciences expands the scope of antioxidant research.

Conclusion

Nowadays, oxidative stress and antioxidants are frequently measured both in various experimental models established in experimental animals (1-14) and in clinical studies (15-21), which is becoming increasingly important. For this reason, oxidant-antioxidant balance indicator parameters are very valuable in scientific research. In addition, newly established different in vivo models have started to measure oxidative stress and antioxidant status (23). For these reasons, our internationally indexed journal TJHS will give priority to scientific research on oxidant-antioxidant balance and publish current scientific developments in this field.

Conflict of interest: There is no conflict of interest.

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Effects of Maternal Vitamin D Deficiency on Osteopenia of Prematurity in Very Low Birth Weight Premature Infants

Çok Düşük Doğum Ağırlıklı Prematüre Bebeklerde Maternal D Vitamini Eksikliğinin Prematüre Osteopenisi Üzerine Etkileri

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Received: 12/08/2021

Accepted: 15/11/2021

Published Online: 02/12/2021

Abstract

Aim: This study aimed to evaluate the effects of maternal vitamin D deficiency on osteopenia of prematurity in very low birth weight premature infants.

Methods: This study was conducted on 60 premature infants born before 32 weeks of gestation with a birth weight < 1,500 g. Infants whose mothers had a 25-hydroxycholecalciferol (25-OHD) level < 40 nmol/L were assigned to group 1 (n = 30), while those with a 25-OHD level ≥ 40 nmol/L were assigned to group 2 (n = 30). Serum calcium, phosphate, and alkaline phosphatase (ALP) levels were measured on the first postnatal day, and weekly during hospitalization. Tubular phosphate reabsorption (TRP), femoral radiographs, and serum urea, creatinine, calcium, phosphate, and ALP were evaluated after 40 weeks of gestation. Two values of ALP > 800 IU/L, at least 1 week apart, was considered diagnostic of osteopenia.

Results: Osteopenia of prematurity was detected in five patients (16.7%) in group 1, and two patients (6.7%) in group 2. No statistically significant differences were found between the two groups, except for lower phosphate levels in group 1 (p = 0.04).

Conclusions: Macro-mineral deficiencies could play a key role in the development of osteopenia of prematurity. Maternal vitamin D deficiencies can have a negative impact on bone metabolism and phosphate levels in infants.

Keywords: Prematurity, osteopenia of prematurity, vitamin D deficiency

Özet

Amaç: Çok düşük doğum ağırlıklı prematüre bebeklerde, maternal vitamin D eksikliğinin prematüre osteopenisi üzerindeki etkilerini değerlendirmek.

Gereç ve Yöntem: Bu çalışma, 32. gebelik haftasından önce doğan ve doğum ağırlığı < 1.500 g olan 60 prematüre bebek üzerinde gerçekleştirildi. Annelerinde 25-OH D vitamini düzeyi <40 nmol/L olan bebekler "grup 1" (n=30), ≥40 nmol/L olan bebekler ise "grup 2" (n= 30) olarak gruplandırıldı. Serum kalsiyum, fosfor ve alkalen fosfataz (ALP) seviyeleri doğum sonrası ilk gün ve hastanede yatış süresince haftalık olarak ölçüldü. Bebekler 40. gebelik haftalarını tamamladıklarında tübüler fosfor geri emilimi, femur radyografileri, serum üre, kreatinin, kalsiyum, fosfor ve ALP düzeyleri değerlendirildi. En az bir hafta arayla alınan iki ALP değerinin > 800 IU/L olması osteopeni tanısı için anlamlı olarak kabul edildi.

Bulgular: Grup 1'deki 5 hastada (%16,7), grup 2'deki 2 hastada (%6.7) prematüre osteopenisi saptandı. Her iki grup arasında prematüre osteopenisi gelişimi açısından fark saptanmadığı ancak 40. gebelik haftasındaki serum fosfor düzeylerinin grup 1'deki bebeklerde daha düşük olduğu (p= 0,04) görüldü.

Sonuç: Prematüre osteopenisinin gelişiminde makro-mineral eksikliği önemli rol oynamaktadır. Maternal D vitamini eksikliği, prematüre bebeklerin kemik metabolizması ve serum fosfor seviyeleri üzerinde olumsuz bir etkiye sahip olabilir.

Anahtar Kelimeler: Prematürite, Prematüre osteopenisi, D vitamini eksikliği

Cite this article: Dursun M., Kavuncuoglu S. Effects of Maternal Vitamin D Deficiency on Osteopenia of Prematurity in Very Low Birth Weight Premature Infants. Turk J Health S. 2021;2(3):pp.31-35.



Introduction

A reduction in the mortality rate of very low birth weight premature infants has led to an increase in prematurity-related diseases (1). One of these diseases is osteopenia of prematurity, which manifests as decreased bone mineralization and, in severe cases, bone fractures (1, 2).

Intrauterine bone mineralization occurs mainly during the third trimester of pregnancy. Deficient bone growth and mineralization are evident in premature infants (3). Increased postnatal nutritional requirements and conditions that prevent mineralization (e.g., delayed nutrition, malnutrition, and steroid therapy) may also contribute to osteopenia of prematurity (4).

The incidence of osteopenia is negatively correlated with birth weight and gestational age, and positively correlated with postnatal morbidities, such as bronchopulmonary dysplasia, necrotizing enterocolitis, and cholestasis (3). The reported prevalence is 20–32% in infants with a birth weight < 1,500 g, and up to 50% in infants with a birth weight < 1,000 g. A higher prevalence has also been reported in breast-fed and soy formula-fed premature infants (2,5).

The prevention and treatment of bone pathologies is a fundamental component of preterm-infant care. Normal bone growth requires adequate and balanced amounts of energy, proteins, vitamins, calcium, phosphorus, and other nutrients (6). Placental transfer, breast milk, and exposure to sunlight for cutaneous biosynthesis are important sources of vitamin D.

During the first 8 weeks of life, the serum 25-hydroxycholecalciferol (25-OHD) levels of infants and their mothers are similar. Due to sociocultural conditions and dietary habits, a high prevalence of maternal vitamin D deficiency has been reported in Turkey (7, 8).

The objective of this study was to evaluate the effects of maternal vitamin D deficiency on osteopenia of prematurity.

Material and Methods

This study is a single center, prospective and case-controlled. The study was carried out on 60 premature babies with a birth weight of <1500 g and born before 32 GW, who were hospitalized in the neonatal intensive care unit of Istanbul Bakırköy Maternity and Child Diseases Training and Research Hospital over a period of 8 months.

Infants with congenital anomalies, exitus before 40 GW after birth, incomplete data, or referral to another hospital were excluded from the study. The 25-OHD levels were measured in the mothers of the included infants. Infants of mothers with 25-OHD levels < 40 nmol/L constituted the study group (Group 1), while those with 25-OHD levels \geq 40 nmol/L constituted the control group (Group 2) (9). We recorded perinatal

follow-up information for mothers, birth type, gender, GW, nutritional pattern, duration of total parenteral nutrition (TPN), medication use, need for mechanical ventilation, previous diseases, and length of stay in the intensive care unit.

All patients received elemental calcium (20–60 mg/kg/day) from the first day, and vitamin D (800 IU) from the 14th day after birth. During follow-up, phosphate (1.5–2 mmol/kg/day) was replaced in patients with a serum phosphate level < 5 mg/dL (10). Calcium, phosphate, and alkaline phosphatase (ALP) levels were measured at 7–14-day intervals to assess the development of osteopenia of prematurity. Breast milk enhancers were advised for patients with enteral nutrition > 90 mL/kg/day. Breast milk-fed infants were advised to continue with breast milk enhancers, while infants who were not fed breast milk were advised to be fed with preterm formula milk after discharge.

All infants were re-examined after 40 GW. Femur radiographs and blood and urine samples were evaluated.

Blood and urine samples

We collected 2.5 mL blood from the mothers of all infants into dry tubes, and analyzed the samples for serum calcium, phosphate, ALP, and 25-OHD on the first postnatal day. Serum calcium, phosphate, and ALP levels were also analyzed in infants on the first postnatal day. Serum urea, creatinine, calcium, phosphate, ALP, and gamma-glutamyl transferase levels, and urine phosphate and creatinine levels, were analyzed after 40 GW. Tubular phosphate reabsorption (TRP) percentages were calculated, and bone mineralization was evaluated using femoral radiographs (Table 1).

Table 1. Methods and reference ranges

Laboratory Parameters	Measurement method	Reference range
Serum calcium	O-cresolphthalein complexone	7.6–10.4 mg/dL
Serum phosphate	Molybdate UV	4.5–9.6 mg/dL
ALP	DGKC assay	0–400 U/L
Urea	Urease UV method	10–50 mg/dL
Creatinine	Compensated rate-blanked Jaffe	0.3–0.7 mg/dL
GGT	Szasz stand	5–50 U/L
Urine phosphate	Photometric UV test	40–140 mg/dL
Urine Creatinine	Compensated rate-blanked Jaffe	28–259 mg/dL
25-OHD	Micro-ELISA	< 40 nmol/L (low); \geq 40 nmol/L (normal)

ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; 25-OHD: 25-hydroxycholecalciferol; ELISA: enzyme-linked immunosorbent assay

Calculation of TRP

Urine and serum phosphate and creatinine levels at 40 GW were used to calculate TRP percentages with the formula below.

TRP (% TRP) = $[1 - (\text{urine phosphate} / \text{urine creatinine} \times \text{plasma creatinine} / \text{plasma phosphate})] \times 100$

Tubular phosphorus reabsorption was found to be increased by $\geq 95\%$ (11).

Assessment of femur radiographs

Femur radiographs were obtained using the Seldix 550 device (Siemens AG, Munich, Germany) at 40 GW, and the radiographs were interpreted by the same radiologist using the scale suggested by Koo et al. (12).

Two ALP levels > 800 IU/mL, at least 1 week apart, were considered diagnostic of osteopenia (13). The parents of all infants were informed about the purpose of the study, and written consent was obtained. This study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from the ethics committee of Istanbul Bakırköy Maternity and Child Diseases Training and Research Hospital.

Statistical analysis

Statistical analyses were performed using NCSS 2007 and PASS 2008 statistical software (NCSS LLC., Kaysville, UT, USA). In addition to descriptive statistics (means and standard deviations), Student's t-test was used to compare two groups with normal distributions. Groups with non-normal distribution were compared using the Mann-Whitney U test. Chi-square and Fisher's exact tests were used for comparison of qualitative data. The alpha threshold was set at 0.05.

Results

In this study, 30 infants with a mean gestational age of 30.3 ± 1.23 (range: 24–32) weeks were included in group 1 and 30 infants with a mean gestational age of 29.73 ± 1.56 (range: 25–32) weeks were included in group 2. In group 1, 14 infants were males and 24 were born by cesarean delivery; in group 2, 16 infants were males and 25 were born by cesarean delivery. Groups 1 and 2 had six and nine infants with birth weights $< 1,000$ g, respectively. There were no differences in maternal characteristics between the groups (maternal age, pregnancy follow-up, presence of preeclampsia, or maternal serum calcium, phosphate, or ALP levels).

The demographic characteristics and clinical data of both groups are shown in Table 2. There were no differences between the groups in diseases encountered during the hospital stay or drugs that could contribute to osteopenia of prematurity (Table 3).

There were no differences between the groups in first-day serum calcium, phosphorus, or ALP levels (Table 4). Osteopenia of prematurity was diagnosed in five patients (16.7%) in group 1 and two patients (6.7%) in group 2. There were no significant differences in the development of osteopenia of prematurity between the two groups.

There were no differences in serum calcium, ALP, gamma-glutamyl transferase, or TRP levels between the two groups at 40 GW. However, serum phosphate levels were lower in group 1 compared to group 2 ($p = 0.04$) (Table 5). Femur radiographs revealed stage 1 osteopenia in two patients in group 1.

Table 2. Demographic characteristics and clinical data

	Group 1	Group 2	p-value
	Mean \pm SD	Mean \pm SD	
Gestational age (weeks)	30.3 \pm 1.23	29.73 \pm 1.56	0.335
Birth weight (g)	1216.67 \pm 247.97	1141.67 \pm 275.35	0.272
Length of hospital stay (days)	35.80 \pm 19.65	38.43 \pm 19.13	0.601
Achievement time of full enteral feeding (days)	22.20 \pm 16.58	20.23 \pm 12.83	0.609
Duration of TPN infusion (days)	17.17 \pm 12.87	16.46 \pm 11.15	0.823
	n (%)	n (%)	p-value++
Antenatal steroid use	18 (60.0%)	21 (70.0%)	0.417
Cesarean delivery	24 (80%)	25 (83.3%)	0.739
SGA	11 (36.6%)	13 (43.3%)	0.87

+ Student t test, ++ Chi-square test, TPN: total parenteral nutrition; SGA: small for gestational age; SD: standard deviation

Table 3. Previous diseases and medication use

	Group 1 (n = 30)	Group 2 (n = 30)	p-value
	n (%)	n (%)	
Sepsis (n = 31)	16 (53.3%)	15 (50.0%)	0.796
NEC (n = 8)	5 (16.7%)	3 (10.0%)	0.706
BPD (n = 14)	4 (13.3%)	10 (33.3%)	0.067
IVH (n = 8)	4 (13.3%)	4 (13.3%)	1.000
PDA (n = 9)	4 (13.3%)	5 (16.7%)	1.000
RDS (n = 29)	11 (36.7%)	18 (60.0%)	0.071
Steroids (n = 9)	3 (10%)	6 (20%)	0.472
Diuretics (n = 13)	7 (23.3%)	6 (20.0%)	0.754
Methylxanthine (n = 35)	17 (56.7%)	18 (60.0%)	0.793

Chi-square test or Fisher's exact test was used, NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus; RDS: respiratory distress syndrome

Table 4. First-day calcium, phosphate, and alkaline phosphatase levels

	Group 1	Group 2	p-value
	Mean \pm SD	Mean \pm SD	
Calcium (mg/dL)	8.35 \pm 0.96	8.42 \pm 1.07	0.791
Phosphate (mg/dL)	5.07 \pm 1.54	4.83 \pm 1.60	0.563
Alkaline phosphatase (U/L)	209.36 \pm 107.51	174.20 \pm 65.15	0.131

Student's t-test was used. SD: standard deviation.

Table 5. Calcium, phosphate, ALP, GGT, and TRP levels at 40 GW

40-week parameters	Group 1	Group 2	p-value
	Mean \pm SD (median)	Mean \pm SD (median)	
Calcium (mg/dL)	9.65 \pm 0.36	9.60 \pm 0.41	0.642
Phosphate (mg/dL)	5.42 \pm 1.12	5.97 \pm 0.88	0.040
ALP (U/L)	458.23 \pm 184.25	414.73 \pm 154.40	0.326
GGT (U/L)	72.07 \pm 86.57 (49)	66.46 \pm 81.93 (34)	0.237
TRP (%)	86.67 \pm 7.15	86.40 \pm 6.58	0.881

Student's t-test and the Mann-Whitney U test were used, TRP: tubular reabsorption of phosphate; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase

Discussion

Premature infants have a greater risk of low bone mineral density, and the risk is inversely related to gestational age. Previous studies have reported a variable incidence of osteopenia of prematurity. The incidence may be up to 30% in infants with a birth weight < 1,500 g, and up to 50% in infants with a birth weight < 1,000 g. However, routine use of breast milk enhancers and preterm formula milks, and early aggressive TPN, decreased the incidence to 10–20% in infants with a birth weight < 1,000 g [13]. Aldemir et al. retrospectively evaluated 3,691 premature infants and found that the prevalence of osteopenia was 3.1%. They found that the prevalence rates of osteopenia were 18.4%, 4.8%, and 1% in infants with birth weights < 1,000 g, 1,000–1,249 g, and 1,250–1,999 g, respectively (14). We diagnosed osteopenia in 3 of 15 (20%) infants with a birth weight < 1,000 g, and in 4 of 45 (8.8%) infants with a birth weight 1,000–1,500 g, similar to the previously reported prevalence rates. Regular monitoring of calcium, phosphate, and ALP levels, breast-feeding or preterm formulas, breast milk enhancers, and short-duration TPN all reduce the risk of osteopenia developing in premature infants.

Although osteopenia of prematurity has a multifactorial etiology, macromineral deficiency is the most important factor. Other factors that increase the risk of osteopenia include intrauterine growth restriction, long-term TPN, use of methylxanthine, steroids, or diuretics, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis, cholestasis, immobility, and low breast milk calcium and phosphate levels (15–17). The role of vitamin D in the etiology of osteopenia of prematurity is not completely understood. During the first 8 weeks of life, serum 25-OHD levels of infants are similar to the maternal levels. Due to the sociocultural conditions and dietary habits in Turkey, maternal vitamin D deficiency has a high prevalence (7, 8). In a study of 87 infants, Dijkstra et al. demonstrated lower cord blood 25-OHD and higher serum ALP levels in infants with vitamin D-deficient mothers compared to controls (18). In a study of 126 females of Asian origin by Brooke et al., vitamin D and placebo were administered to 59 and 67 participants during pregnancy,

respectively. Lower 25-OHD and calcium levels, and higher ALP levels, were detected in the babies of mothers in the placebo group compared to the vitamin D group (19). Based on studies that have demonstrated similar maternal and fetal 25-OHD levels, we investigated serum calcium, phosphate, and ALP levels, instead of 25-OHD levels, in infants on the first postnatal day. We did not find any significant differences between the groups.

Serum calcium, phosphate, and ALP levels are commonly used in the diagnosis of osteopenia of prematurity. Backström et al. reported that serum ALP levels > 900 U/L were associated with low bone mineral density (sensitivity: 88%; specificity: 71%) (20). Mitchell et al. demonstrated that an isolated increase in ALP level was not associated with radiological findings of rickets and suggested weekly assessment of ALP levels (> 800 IU/L). In our study, two values of ALP > 800 IU/L, at least 1 week apart, in at-risk infants were considered significant. There was no significant difference in the rate of development of osteopenia of prematurity between the two groups.

Some studies have demonstrated normal 25-OHD levels, and normal or raised calcitriol levels, in premature infants diagnosed with osteopenia (21, 22). McIntosh et al. demonstrated normal or high 25-OHD levels in eight infants with a birth weight < 1,000 g (2,000 IU/day vitamin D administered from the 7th day) and radiological findings of rickets, suggesting that vitamin D does not play a role in the development of osteopenia (23). Hillmann et al. demonstrated that in 45% of 72 very low birth weight premature infants, daily vitamin D supplementation (400 IU) over 12 weeks was associated with either no change or a slight increase in vitamin D levels. The remaining 55% of the infants had vitamin D levels < 15 ng/ml. In the same study, vitamin D levels were not found to be correlated with serum calcium, phosphate, or ALP levels during 12 weeks of vitamin supplementation. However, low levels of serum calcium and phosphate, and high levels of ALP, were found in the vitamin D-deficient group after 12 weeks (24). The infants enrolled in our study were re-evaluated at 40 GW, as osteopenia of prematurity becomes clinically apparent at 6–12 weeks (3). The mean serum phosphate level was lower in the vitamin D-deficient than control group ($p = 0.04$), but there were no differences between the two groups in serum calcium or ALP levels, TRP percentages, or radiographical findings in the femur. Maternal vitamin D deficiency may have contributed to the low serum phosphate levels of the group 1 infants.

Although serum calcium, phosphate, and ALP levels are the most commonly used parameters for diagnosing osteopenia of prematurity, they do not have high sensitivity or specificity for osteopenia (1). Studies have demonstrated that very low birth weight preterm infants have lower renal phosphate thresholds and higher urinary phosphate excretion rates than term infants,

even in the presence of low serum phosphate levels (24, 25). Harrison et al. suggested that the TRP percentage was the best indicator of the adequacy of phosphate supplementation, and TRP percentages > 95% indicated insufficient supplementation. That study recommended that TRP levels be monitored in cases with ALP > 500 IU/L and phosphate < 1.8 mmol/L (5.5 mg/dL) (11). We measured the TRP levels after 40 GW because earlier measurements may be inaccurate. No statistically significant differences were found in TRP levels between the groups despite the low serum phosphate levels in group 1. However, these findings may be unreliable due to the small sample size of our study.

The limitations of this study included a short study period and small number of patients. Furthermore, the number of infants with a birth weight < 1,000 g, who are at the greatest risk of osteopenia of prematurity, was lower than the number of infants with a birth weight of 1,000–1,500 g. The lack of a consensus definition for the diagnosis of osteopenia of prematurity, the inadequacy of biochemical parameters and radiological imaging to diagnose osteopenia, and the use of different reference ranges for 25-OH vitamin D can be counted as other limitations.

Conclusions

In conclusion, macro-mineral deficiencies may play a key role in the development of osteopenia of prematurity. Maternal vitamin D deficiency appears to have a negative impact on bone metabolism and phosphate levels in infants. Further studies with larger samples of very low birth weight infants are required to explore this subject in more depth.

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Internal Limiting Membrane Flap Transplantation into the Optic Disc Pit with Two Different Internal Limiting Membrane Peeling Techniques in Optic Disc Pit Maculopathy

Optik Disk Pit Makülopatide İki Farklı İç Sınırlayıcı Membran Soyma Tekniği ile Optik Disk Pit'e İç Sınırlayıcı Membran Flep Transplantasyonu

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Received: 01/08/2021

Accepted: 14/11/2021

Published Online: 02/12/2021

Abstract

Purpose: To report four patients with optic disc pit-maculopathy (ODP-M) treated with transplantation of internal limiting membrane (ILM) flap, obtained by two different ILM peeling techniques, into the optic disc pit (ODP).

Method and Patients: One eye of 4 patients with ODP-M underwent 23 gauge pars plana vitrectomy. Three patients underwent ILM peeling, free ILM flap transplantation to ODP, and 15-17% perfluoropropane (C3F8) gas tamponade. In these 3 patients, the ILM was transplanted to ODP after complete peeling. In one patient, the nasal fragment of the ILM was left unpeeled and then the peeled ILM flap was folded over the unpeeled portion and transplanted into ODP.

Results: Serous macular detachment and intraretinal multilayered fluid regressed at the end of the postoperative 3rd month in all cases. In all patients, macular thickness decreased and best-corrected visual acuity (BCVA) increased in the postoperative 3rd month. An unexpected macular hole (MH) developed in two patients (Case 2, 3). In one of these patients, MH was closed by peeling the wider ILM, and it was observed that BCVA increased.

Conclusions: ILM flap transplantation to ODP has been observed as an effective surgical technique for the treatment of ODP-M. In addition, a wider ILM peeling was observed to be effective in closure of the permanent MH that developed after ILM transplantation to ODP.

Keywords: Optic disc pit; Optic disc pit-maculopathy, Inverted internal limiting membrane flap transplantation; Free internal limiting membrane flap transplantation; Macular hole

Özet

Amaç: İki farklı iç sınırlayıcı membran (İSM) soyma tekniği ile elde edilen İSM flebinin optik disk pit'e (ODP) transplantasyonu yapılarak tedavi edilen optik disk pit-makülopatili (ODP-M'li) dört hastanın sunumu.

Metod ve Hastalar: ODP-M'li 4 hastanın bir gözüne 23 gauge pars plana vitrektomi uygulandı. Üç hastaya İSM soyulması, ODP'e serbest İSM flep transplantasyonu ve %15-17 perfloropropan (C3F8) gaz tamponadı uygulandı. Bu 3 hastada, İSM tamamen soyulduktan sonra ODP'e transplante edildi. Bir hastada, İSM'nin nazal parçası soyulmadan bırakıldıktan sonra İSM'nin soyulmuş parçası soyulmamış kısım üzerine katlanarak ODP'e transplante edildi.

Bulgular: Tüm olgularda postoperatif 3. ayın sonunda seröz makula dekolmanı ve intraretinal çok tabakalı sıvı geriledi. Ameliyat sonrası 3. ayda tüm hastalarda makula kalınlığı azaldı ve en iyi düzeltilmiş görme keskinliği (EİDGK) arttı. İki hastada (Olgu 2, 3) beklenmedik bir makula deliği (MD) gelişti. Bu hastalardan birinde daha geniş İSM soyulmasıyla MD kapandığı ve EİDGK'nin arttığı gözlemlendi.

Sonuçlar: ODP'e İSM flep transplantasyonu, ODP-M tedavisinde etkili bir cerrahi teknik olarak gözlenmiştir. Ayrıca ODP'e İSM transplantasyonu sonrası gelişen kalıcı MD'in kapatılmasında ikincil daha geniş İSM soyulmasının etkili olduğu gözlemlendi.

Anahtar Kelimeler: Optik disk pit; Optik disk pit-makülopati, Kıvrılmış iç sınırlayıcı membran flebi transplantasyonu; Serbest iç sınırlayıcı membran flebi transplantasyonu; Makula deliği

Cite this article: Kucuk MF., Erol MK. Internal Limiting Membrane Flap Transplantation into the Optic Disc Pit with Two Different Internal Limiting Membrane Peeling Techniques in Optic Disc Pit Maculopathy. Turk J Health S. 2021;2(3):pp.36-41.



Introduction

Optic disc pit (ODP) is a cavitation caused by a congenital developmental defect in the optic disc (OD) [1]. 25-75% of ODP cases develop maculopathy in which the retinal pigment epithelial layer changes after the accumulation of fluid in the retinal layers and / or subretinal region [2, 3]. The origin of the fluid in optic disc pit-maculopathy (ODP-M) is controversial [4, 5]. The debate over ODP-M began with the ODP-M study of K.T.A Halbertsman (1927), who claimed that maculopathy, reported by James in 1913, did not develop due to ODP [6].

ODP-M usually occurs between the ages of 30 and 40 [7], but has also been reported in children [8]. Best-corrected visual acuity (BCVA) regresses up to 20/70 or even more [9]. Patients with a reduction in BCVA of up to 20/200 have been reported, as well as patients with spontaneous improvement [10]. Although surgical treatment is discussed, there are also clinics where different surgical procedures are performed due to the development of significant vision loss in many untreated cases [10, 11]. Because of the importance of vitreopapillary traction in ODP development, pars plana vitrectomy (PPV) is currently the most widely accepted treatment modality [1, 12, 13]. Furthermore, treatment methods in addition to PPV are discussed due to the unknown source of the fluid and different clinical approaches [11, 14]. Peeling of the internal limiting membrane (ILM), gas tamponade, temporal endolaser photocoagulation, injection of autologous platelet, temporal-side single radial optic neurotomy, transplantation of an ILM piece to ODP are some of the adjuvant treatments discussed [15-20].

Some recent studies have shown that ILM flap transplantation to ODP is an effective surgical technique. [21-28]. In this study, we present the results of different methods of this new surgical technique, about which there are few studies in the literature.

Methods

Four eyes of four patients with ODP-M were treated and followed up with the technique of ILM flap transplantation to ODP. Informed consent was obtained from each patient regarding the use of clinical data. The study was compliant with the 1964 Helsinki declaration. Pre and postoperative comprehensive eye examinations were performed in all patients, including BCVA, slit lamp biomicroscopy, tonometry measurements, and fundus examinations. Fundus autofluorescence photograph and color fundus photographs were performed with Visucam NM / FA (Carl Zeiss, Germany). Macular thickness (MT) measurements were performed with Cirrus high-resolution (Optical Coherence Tomography) OCT, model 5000 (Carl Zeiss Meditec Inc., Jena, Germany) and OCT-Angiography (OCT-A) were performed using RTvue 100 OCT-A (Optovue Inc., Fremont, CA).

Surgery

In all patients, 23-gauge PPV was performed. In Cases 1, 3 and 4, ILM was peeled from the temporal region of the macula to the temporal edge of the OD, and a small section on the nasal region of the macula was left unpeeled. ILM was then transplanted into ODP by inverting the flap, which we named 'inverted ILM flap transplantation' (IILMFT). In Case 2, ILM was completely peeled and transplanted into ODP, which we named 'free ILM flap transplantation' (FILMFT). In Cases 2 and 3, a single-row macular barrier endolaser (MBEL) was applied to the nasal region of the macula. Finally, gas tamponade (15-17% C3F8) was performed in all eyes. All the cases were operated on by the same surgeon.

Case 1

Preoperative findings: At the first examination of the 38-year-old male patient, BCVA in the left eye was 20/63. ODP, serous macular detachment (SMD) and intraretinal multilayered fluid (IMLF) were detected in the left eye. The patient was diagnosed with ODP-M in his left eye. The MT was 685 μ in the most raised area. After 13 weeks of follow-up, surgery was planned when BCVA regressed to 20/200, SMD increased, and MT increased to 990 μ (Figure 1a-d).

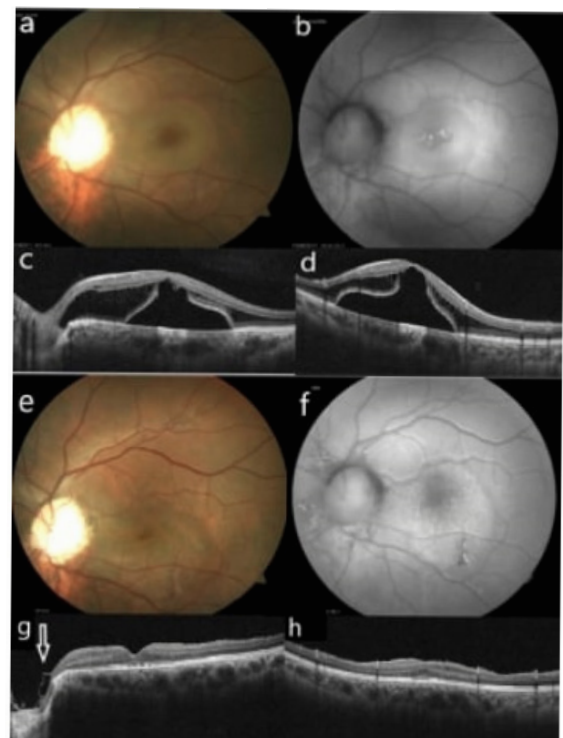


Figure 1. Preoperative color fundus (a), autofluorescence (b), OCT images (c, d) of Case 1. ODP, SMD, IMLF are seen in a, b, c and d images. Postoperative color fundus (e), autofluorescence (f), OCT images (g, h) of Case 1. Color fundus and autofluorescence were obtained at week 47, OCT images at week 96 postoperatively. ILM flap (white arrow) plugged into ODP is seen (g). Surgical technique: IILMFT

Case 2

Preoperative findings: At the first examination of an 11-year-old female patient, BCVA was 20/200 in the left eye. Based

on the presence of ODP, SMD, and IMLF in the left eye, she was diagnosed with ODP-M. Six weeks later, when BCVA decreased to 20/400 and the MT increased to 1036 μ , surgery was planned (Figure 2a-d).

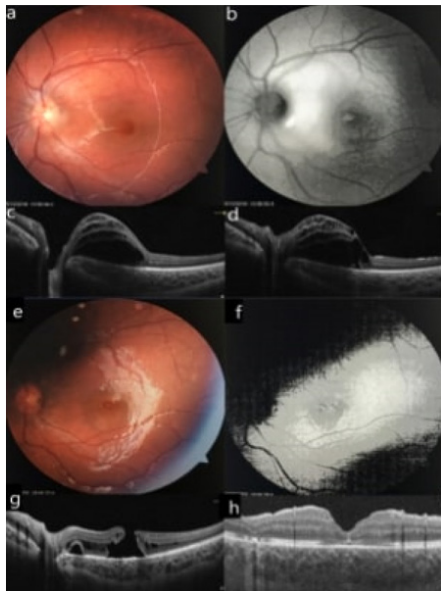


Figure 2. Preoperative color fundus (a), autofluorescence (b), OCT images (c, d) of Case 2. ODP, wide SMD, and IMLF are seen in a, b, c and d images. Postoperative color fundus (e), autofluorescence (f), OCT images (g, h) of Case 2. Macular hole development is seen in the color fundus (e), autofluorescence (f) and OCT images (g) at the postoperative 20th week. OCT image (h) after the second operation shows that the macular hole is closed. Surgical technique: FILMFT and MBEL during the first operation, and wider ILM peeling during the second operation.

Case 3

Preoperative findings: At the first examination of a 44-year-old female patient, BCVA was 20/200, and SMD and IMLF were detected in the left eye with ODP. Therefore, the patient was diagnosed with ODP-M. Six weeks later, surgical treatment was planned when SMD and the MT increased and BCVA decreased to 20/400 (Figure 3a-d).

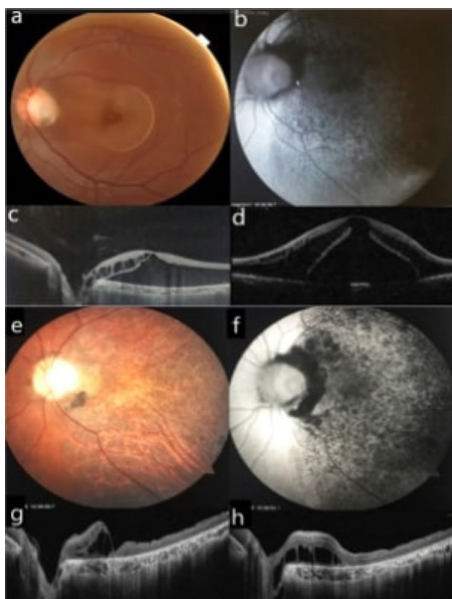


Figure 3. Preoperative color fundus (a), autofluorescence (b), optical coherence

tomography images (c, d) of Case 3. ODP, SMD, and IMLF are seen in a, b, c and d images. Postoperative color fundus (e), autofluorescence (f), optical coherence tomography images (g, h) of Case 3. e, f, g, h images were obtained at 52 weeks postoperatively and they show disruption in the photoreceptor layer. Surgical technique: IILMFT and MBEL.

Case 4

Preoperative findings: At the first examination of a 24-year-old female patient, BCVA was 20/400, and ODP, SMD, and IMLF were detected in the left eye; thus, the patient was diagnosed with ODP-M. Additionally, the left eye had a narrowed eyelid at inward gaze, and the fellow eye had restricted outward gaze. After two weeks of follow-up, surgery was scheduled when BCVA decreased to 20/400, the MT increased to 492 μ , and SMD expanded (Figure 4a-d).

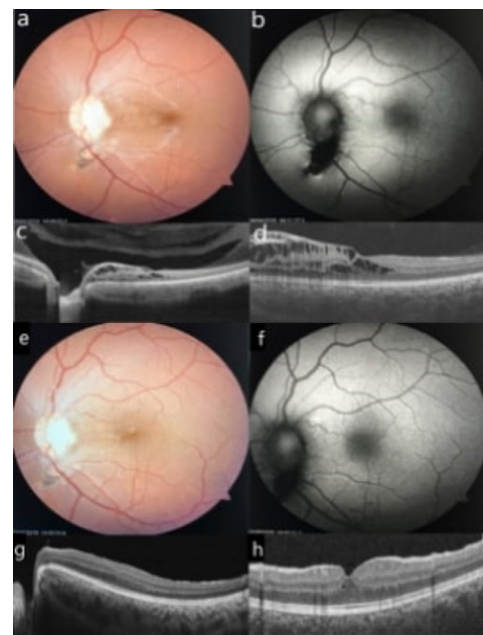


Figure 4. Preoperative color fundus (a), autofluorescence (b), OCT images (c, d) of Case 4. ODP, SMD, and wide IMLF are seen in a, b, c and d images. Postoperative color fundus (e), autofluorescence (f), OCT images (g, h) of Case 4. Color fundus, autofluorescence and OCT images were obtained at 43 weeks postoperatively. Surgical technique: IILMFT

Result

Case 1

Postoperative findings: BCVA was 20/25 at 24 weeks postoperatively. SMD and IMLF disappeared at the 24th week. At the postoperative 96th week, the MT decreased to 303 μ (Figure 1e-h).

Case 2

Postoperative findings: BCVA was 20/50 at the 19th week postoperatively. The MT decreased to 456 μ . SMD and IMLF regressed. However, unexpected macular hole (MH) development was observed at the 20th week. Reoperation was performed at the 25th week due to the persistence of MH. At the 64th week, MH closed, SMD disappeared, the MT decreased to 347 μ , and IMLF was no longer seen (Figure 2e-

h).

Case 3

Postoperative findings

We managed to communicate with the patient at the 52nd postoperative week. BCVA was 10/400, the MT was 619 μ , and SMD and IMLF were evident. Unfortunately, we detected an MH with the atrophy of the photoreceptor layer. This is why we were not able to consider secondary surgery (Figure 3e-h).

Case 4

Postoperative findings

At the postoperative 43rd week, BCVA was 20/25, IMLF and SMD disappeared, and the MT decreased to 342 μ (Figure 4e-h).

Discussion

Combined surgical treatments have been used in the treatment of ODP-M in recent years. Although successful results have been reported with different surgical techniques, controversy continues [14-20]. Vitreopapillary and vitreoretinal traction are important in the pathogenesis of ODP-M, and it is thought that fluid is directed to the retina due to the pressure difference caused by traction [13, 29, 30]. It has been shown that intraretinal and subretinal fluid is reduced in ODP-M after PPV surgery to eliminate traction. Similarly, we detected preoperative vitreopapillary traction in our cases and applied PPV to all patients. While PPV is generally considered the main treatment, most studies have also used adjuvant treatments to PPV. Surgical success, side effects, and possible complications of adjuvant treatments are also controversial. [15-20]. One of the reasons for the controversy is that the source of intraretinal or subretinal fluid is unknown. The goal of most adjuvant therapies is to prevent fluid transfer to the retina. The aim here is based on the hypothesis proposed by Jain and Johnson. In this hypothesis, it is claimed that there is a transition between the extraocular region and the intraocular cavities due to a defect in the lamina cribrosa and/or juxtapapillary sclera [1]. Endolaser treatment is one of the adjuvant treatments. Endolaser is used alone or in combination with other adjuvant treatments in PPV. It has been claimed that endolaser therapy alone does not contribute to anatomical success in PPV [31]. In addition, photocoagulation to the edge of the OD to create a barrier has been criticized for the development of permanent scotoma in the maculopapular bundle [15, 32]. In the current study, while we applied endolaser in 2 of our cases (Case 2-3), we did not apply it in the others. However, we did not observe any anatomical or visual differences between our cases.

Surgical outcomes of ILM peeling are also discussed [17]. ILM peeling is claimed to eliminate tangential traction from the retina and help withdraw fluid from the retina [33]. Marticorena et al. reported the dissolution of ODP-M after ILM

peeling to the patient who failed with PPV, gas tamponade, and endolaser [34]. Wider ILM peeling has been shown to cause reduced retinal sensitivity, foveal tissue thinning, and anatomical damage [17, 33, 35]. In our study, we observed MH development and macular changes in Case 2 and 3. However, in Case 2, we observed that persistent MH that developed after ILM transplant to ODP was closed with wider ILM peeling. Similarly, Sborgia et al observed that ILM peeling was more effective in IMLF [25].

Recently, studies have been conducted on the techniques of ILM flap transplantation to ODP to prevent fluid migration caused by ODP. [20-28]. It is claimed that the ILM flap may be a barrier to prevent fluid passage into and under the retina. In these studies, the ILM flap was transplanted to the ODP with two different techniques. In the first technique, the temporal part of the macula was peeled to include the fovea region, while the nasal part of the macula adjacent to the OD was folded without peeling and transplanted to the ODP (IILMFT). In the second technique, the ILM completely peeled from the macula was transplanted to the ODP as a free flap (FILMFT). In our study, we performed the free flap technique in one of four cases and the inverted flap technique in three cases. Different anatomic and functional results have been reported with these techniques. Pastor-Idoate S. et al suggested that folding of the peeled ILM fragment over the macular region left non-peeled (IILMFT) adjacent to ODP may serve as a scaffold for Müller grade cell proliferation and may induce gliosis [28]. Ravani et al. compared these two different ILM transplantation techniques [26]. There are not many studies comparing their efficacy since it is a rare clinical situation. Studies on ILM transplantation to the ODP are mostly in the form of case reports. Our case series seems to be one of the most reported studies with these techniques.

Many cases of spontaneously resolving ODP-M have been reported in the literature [36-38]. If spontaneous recovery was not observed in the studies, the prognosis was not good for patients who were not treated or not treated in a timely manner [37, 38]. It has been suggested that irreversible changes may develop in the pigment epithelial layer and retinal cells due to chronic SMD and IMLF [37-39]. Although the macula was reattached in these cases, it was observed that there was no improvement in visual functions [37]. As suggested in Bloch's study, the development of SMD and visual impairment may be important clinical findings to prioritize surgery [39]. However, Pastor-Idoate S et al reported that the duration of preoperative symptoms did not affect postoperative macular reattachment [28]. Rayat JS et al., on the other hand, have observed that the retinal pigment epithelium-Bruch membrane complex and photoreceptor cells are damaged in chronic and refractive maculopathies [40]. In addition, Spaide et al. observed that photoreceptor apoptosis and subretinal precipitates

prevent visual recovery in chronic or refractory processes [30]. Similarly, we found chronic retinal degenerative findings in Case 3. In this Case with preoperative low BCVA, postoperative vision improved slightly in the first three months but decreased in the 24th month. In 80% of Pastor-Idoate S. et al's cases, structural recovery was prolonged to one hundred and eighty days. In this study, we observed that the structural improvement in Case 1 reached the twenty-fourth week. In Case 3, subretinal and intraretinal fluid was withdrawn in six months. In our second Case, subretinal fluid was not observed after the closure of the MH with ILM in the second surgery. In our second Case, persistent full-thickness MH developed, similar to that reported by Hara [23] and Navrocki [21]. However, in the second operation, we observed that the MH was closed with the transplantation of the ILM obtained by peeling the wider ILM, and then the vision improved. Muhammed OA et al. [20] and Sborgia G et al. [25] reported that BCVA started to improve in the first month and reached expected high levels in the sixth month. However, Pastor et al [28] found this improvement over a longer period. Caporossi et al. observed both visual and structural improvement at ten months and no recurrence at follow-up [27]. Pastor Idoate et al. [28] reported no recurrence within six to twelve months of the follow-up period. Two of the three cases presented by Nawrocki et al [21] were reoperated for recurrence. Pastor et al [28] stated that they did not see the desired level of functional improvement (44%) in the long term in chronic and refractive cases. However, in our study, we observed that BCVA increased as the follow-up periods increased in the first year.

Large case series and long follow-up studies are needed to be considered as successful adjuvant techniques and to compare these techniques. However, in such rare clinical situations, this will not be easy. There are few published studies that we have seen to date and that there are not enough patients in the studies.

In conclusion, ILM flap transplantation to ODP has been observed as an effective surgical technique for the treatment of ODP-M. In addition, a wider ILM peeling was observed to be effective in closure of the permanent MH that developed after ILM transplantation to ODP.

Financial disclosures

The authors have no financial or ownership rights over a product, method, or material mentioned herein.

Declaration of interest

The authors reported no conflict of interest and the authors are solely responsible for the content and writing of the article.

Funding

All Authors declare that they do not receive financial support from any foundation, public or private source.

Ethical approval

Ethical standards All procedures performed in studies involving human participants comply with the ethical standards of the national research committee and the 1964 Declaration of Helsinki and subsequent amendments.

Informed consent

Informed consent was obtained from all patients included in the study.

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Effects of Health Policies on the COVID-19 Process

Sağlık Politikalarının COVID-19 Sürecine Etkileri

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Received: 30/06/2021

Accepted: 01/10/2021

Published Online: 02/11/2021

Abstract

Aim: Many people around the world are still affected by coronavirus (COVID-19) disease. The high spread rate of the COVID-19 and the number of deaths make it more important than ever to understand the behavior of the disease. In this work, the effects of health policies on the COVID-19 process is examined by taking into account various data.

Material and Methods: Official articles, circulars issued by decision makers, Worldometer and Our World in Data websites are used to study the effects of the health policies on the COVID-19 process from 10.03.2020 to 30.06.2021. The scenario in which the appropriate precautions were not taken by decision makers is also considered by simulating data with the method of least squares.

Results: It has been determined that the measures taken have positive effects with a delay of 12-15 days. We observe that the policies adopted for the COVID-19 process are effective in reducing the number of cases and deaths. We note that there were increases in the number of cases after the removal of some measures. Overall, Turkey's situation in terms of total case and mortality rates in COVID-19 process is better than the average of some European and neighboring countries.

Conclusion: The results shows that Turkey has quite disciplined and successful health policy to overcome coronavirus disease.

Keywords: COVID-19, modelling, least squares method, health policy, Turkey

Özet

Amaç: Dünya çapında çok sayıda insan hala COVID-19 sürecinden etkilenmektedir. Pandeminin yüksek yayılma hızı ve ölüm sayısı, hastalığın davranışını/seyrini anlamayı her zamankinden daha önemli hale getirmektedir. Bu çalışmada, uygulanan sağlık politikalarının COVID-19 sürecine etkileri incelenmiştir.

Materyal ve Metod: Türkiye'de virüsün ortaya çıktığı 10.03.2020 ile 30.06.2021 tarihleri arasındaki süreçte uygulanan sağlık politikalarının COVID-19 sürecine etkisinin araştırılması için ilgili yönetim organları tarafından çıkarılan genelge ve resmi yazılar ile Worldometer ve Our World In Data internet sitesi kullanılmıştır. Söz konusu politikaların uygulanmaması durumunda karşılaşılabilecek tabloya ilişkin modellemeler en küçük kareler yöntemi kullanılarak grafiğe dönüştürülmüştür.

Bulgular: Alınan önlemlerin 12-15 gün gecikmeli olarak olumlu etkilerinin olduğu gözlemlenmektedir. Covid-19 sürecine yönelik benimsenen politikaların vaka ve ölüm sayılarının azalmasında etkili olduğu görülmektedir. Bazı kısıtlamaların kaldırılmasıyla vaka sayılarında artışlar olmakla birlikte, sonuç olarak, Türkiye'nin durumunun toplam vaka ve ölüm oranları bakımından bazı Avrupa ülkeleri ile komşu ülkelere göre daha olumlu olduğu tespit edilmiştir.

Sonuç: Sonuçlar, Türkiye'nin koronavirüs hastalığını yenmek için oldukça disiplinli ve başarılı bir sağlık politikasına sahip olduğunu göstermektedir.

Anahtar Kelimeler: Covid-19, modelleme, en küçük kareler yöntemi, sağlık politikası, Türkiye

Cite this article: Sendur A., Cakir Z., Sozen ME. Effects of Health Policies on the COVID-19 Process. Turk J Health S. 2021;2(3):pp.42-48.



1. Introduction

The coronavirus disease 2019 (COVID-19), which was first seen in the city of Wuhan (China) at the end of December-2019 and spread rapidly all over the world, has been announced as an international pandemic by the World Health Organization (WHO) in March-2020 [1, 2]. So far, the pandemic in China appears to be basically under control, but many people around the world are still affected. The high spread rate of the pandemic and the number of deaths make that more important than ever to understand the current mathematical models. For this reason, the course of the disease (the rate of spread, duration of the disease, etc.) and its possible effects are among the most discussed and studied subjects by scientists in all countries around the world [3, 4, 5].

In the initial phase of COVID-19, countries have developed different policies in the health sector [6, 7]. In this context, countries generally adopted suppression or pacification strategies [8, 9]. The suppression strategy is a policy in which the government is effective and various restrictive measures are taken. On the other hand, the pacification strategy is characterized by slowing down the pandemic in the long term and protecting certain groups against the pandemic during periods when the need for health services is high [8, 10]. Turkey has adopted the suppression strategy and several restrictions have been applied in this context. In addition, the coronavirus scientific committee and filtration teams were formed, pandemic hospitals and the characteristics of these hospitals were determined. Moreover, financial support to the health system has been increased and government support has been provided strongly for vaccine studies.

This study aims to investigate the effect of health policies in the process of managing the COVID-19 pandemic in Turkey on components such as total number of cases, number of daily cases, total death, daily death, number of active cases, and number of cases at risk of death. In the study, especially critical dates regarding the policies applied during the pandemic process are discussed. The determinations are made by applying the sources such as circulars and official articles issued by decision makers, Worldometer and Our World in Data websites [11, 12]. The study consists of the data and health policies applied during the COVID-19 process from 10.03.2020 to 30.06.2021.

2. Material and Methods

2.1. The COVID-19 Process and Policies

In this section, we summarize some critical measures and decisions during the COVID-19 pandemic process for Turkey in chronological order in Table 1.

2.2. Effects of Adopted Policies on the Course of the Pandemic

In this section, the impact of the policies adopted during the COVID-19 process on the course of the pandemic in terms of various variables (such as daily number of cases, daily deaths, number of active cases and number of cases at risk of death) are examined and some inferences are made by taking into account some critical measures, decisions, and implementations on the dates indicated in Table 1. In order to visualize the data more clearly with graphics, we extend the timeline by including the dates before and after the critical decisions. Simulations when the mentioned policies are not implemented have also been discussed by applying the method of least-squares using appropriate polynomials [13] and converted into graphs via Microsoft Excel.

2.3. A Comparison of Some Developed Countries with Turkey

In this section, we aim to investigate the struggle in Turkey with a reliable and holistic approach. Therefore, the situation in Turkey during the fight against COVID-19 is compared with the developed countries of Europe or neighboring countries such as Russia and Iran in terms of the indicators such as the rates of total number of cases and deaths.

3. Results

3.1. Effects of Adopted Policies on the Course of the Pandemic

The impact of the policies adopted during the COVID-19 process on the course of the pandemic in terms of various variables are examined. In order to visualize the data more clearly, the timeline is extended including the dates before and after the critical decisions

3.1.1. Effects of Decisions on Daily Cases and Deaths

In Figure 1, we observe that the policies which were taken on 3-4 April 2020 and implemented as a curfew on 11, 17-19 April 2020 reduced the rapid increasing number of cases and deaths since mid-March and showed a positive effect with a delay of 12-15 days. The number of daily cases, which was 5138, decreased to around 2600 at the end of April by taking appropriate precautions. In Figure 1, we also focus on the case: What would happen if the precautions were not taken? According to the linear simulation by the method of least squares, the number of daily cases could reach over 8000 at the end of April if there were not any precautions and if the increasing trend that started in mid-March was continued. In addition, the number of daily deaths was under 100 at the end of April which could exceed 200 if there were not any precautions. We note that, the simulation is obtained by extending the behavior of actual data from March 25 to April 11, 2020, beyond April 11, 2020.

Table 1. The timeline of the decisions and practices to take the COVID-19 pandemic under control in Turkey (The dates were collected by following the reports from the Republic of Turkey Ministry of Health)

Date	Event
10.Mar.20	The first coronavirus case in Turkey.
14.Mar.20	Stopping the two-way flights to Germany, France, Spain, Norway, Denmark, Belgium, Austria, Sweden and Netherlands unilaterally from 08:00 on 14 March until 17 April 2020.
15.Mar.20	Stopping Umrah departures as of February 27, 2020, and planning for an early return for citizens who have already gone.
16.Mar.20	Taking a break in primary, secondary and high school education for one week and university education for three weeks.
23.Mar.20	Initiation of administration of the favipiravir to patients in intensive care.
24.Mar.20	All local and intercity public transportation vehicles, accepting passengers at a rate of 50% of the passenger carrying capacity specified in the vehicle license for a temporary period.
25.Mar.20	Extension of the break in education until April 30, 2020.
3.Apr.20	Expanding the scope of the curfew: imposing a curfew for those born on January 1, 2000 and above, introducing a mask requirement in public areas such as markets and bazaar. Suspension of entry and exit from 30 metropolitan cities and Zonguldak for 15 days.
4.Apr.20	Turkish Airlines' domestic flights were suspended until 20 April 2020.
11.Apr.20	Comprehensive curfew: Declaring a curfew in 30 metropolitan cities and Zonguldak for 48 hours starting from 00:00 on Saturday, April 11, 2020.
	Implementation of the same curfew decision for 17-19 April 2020 and 22-26 April 2020.
4.May.20	Partial prohibitions: Controlled Social Life.
1.Jun.20	After the first period of the measures, the removal of certain bans starting from 1 June 2020.
26.Aug.20	Allowing alternate, flexible and remote working in public institutions and organizations.
21.Sep.20	The beginning of face-to-face education in kindergarten and primary school (1st grades).
12.Oct.20	Opening of all primary schools, village schools, 8th and 12th grades and schools for children with special needs.
18.Nov.20	Restrictions and the introduction of various prohibitions again
25.Nov.20	Initiation of disclosure of previously unexplained asymptomatic (asymptomatic, mild) cases.
13.Jan.21	Approval for emergency use of CoronaVac vaccine in Turkey.
1.Mar.21	Application of the on-site decision period within the scope of controlled normalization. Categorizing the provinces in four different risk groups (low, medium, high, very high).
	Cancellation of the ban on people over 65 and under 20 years old, starting education at all education levels, and cancellation of the weekend curfew in low and medium-risk cities. In high and very high-risk cities, only 8, 12, primary schools and pre-school education institutions are opened. Increasing the curfew period for those over 65 and under 20 years old. Businesses such as cafes and restaurants starting to accept customers again with 50% capacity in all provinces except very high-risk provinces. Continuation of the curfew between 21.00-05.00 throughout Turkey.
29.Mar.21	58 provinces turning into very high-risk groups, reintroducing weekend curfews.
2.Apr.21	Application of the first dose of Biontech vaccine in Turkey.
14.Apr.21	Extending restrictions: Two-weeks partial closure implementation. Limitation in many areas, especially the curfew implementation between 19.00-05.00 on weekdays and the entire weekend.
26.Apr.21	Suspension of education at all levels and postponement of exams to a later date.
29.Apr.21	Announcement of full closure until May 17, 05:00. Suspension of education at all levels and postponement of exams. Announcement that intercity public transportation vehicles will operate at 50% capacity. Announcement that chain markets will be closed on Sunday.
4.May.21	The number of vaccines made in Turkey exceeds 23 million doses.
16.May.21	Curfew between 21.00-05.00 on weekdays and full day on weekends. Cancellation of the curfew for citizens under age 18 and aged 65 years old who has received two doses of vaccination. Prohibition of using public transport for citizens under 18 and over 65 years old, regardless of whether they are exempt from the restriction. Opening of shopping centers between 10.00-20.00 on weekdays and completely closed on weekends. Extension of the current visitor restriction in social protection/care centers such as nursing homes, rehabilitation centers, children's homes until June 1, 2021. Starting of international flights from abroad to Turkey.

In Figure 2, we observe the continuity of the decreasing trend (starting around mid April) in the number of daily cases and deaths until the end of May despite the controlled social life policies on May 4, 2020. Although there was a partial increase after the removal of certain bans on June 1, 2020, the number of daily cases and deaths was within controllable limits with the adaption of the controlled social life. In Figure 3, we also focus on the situation if the administrative implementations continued in a similar way. The linear simulation obtained by the method of least squares shows that the number of daily cases, which were around 1200, could be around 800, and the

number of daily deaths due to COVID-19 could be lower than actual data.

Decisions such as “Allowing alternate, flexible and remote work in public institutions and organizations - August 26, 2020”, and “Starting face-to-face education in kindergarten and primary school (1st grades) - September 21, 2020” caused a slight increase in the number of daily cases and deaths from the beginning of October 2020. With the decision of “opening all primary schools, village schools, schools for 8th and 12th grades and children with special needs - October 12, 2020”, the increasing trend accelerated, and the number of daily cases

were around 2200 and the number of daily deaths were at the level of 75 by the end of October 2020. In order to control this situation, a couple of decisions including various restrictions and prohibitions were taken on November 18, 2020 and therefore a favorable process continued until the beginning of March 2021 with the sensibility of the society on obeying the recommendations. After the “controlled normalization” decision on March 1, 2021, the number of cases and deaths increased again and the cases on a daily basis reached to 63000 and deaths to over 350 by mid-April 2021.



Figure 1. (a) The impact of the decisions (3-4 April 2020) on the number of daily cases. (b) The impact of the decisions (3-4 April 2020) on the number of daily deaths

Here, we also focus on the case: What would happen if the administrative implementations and social reflexes until March 1, 2021, continued in a similar way? Using the actual data from January 15 to March 1, 2021 for the method of least squares with quadratic polynomials, we observe that the number of cases might be around 15000 instead of 40000 and the number of deaths at the level of 50 instead of 180 by the end of March 2021 (Figure 4. (a)-(b)).

The reimposition of the curfew on the weekend of 29 March 2021 did not provide the desired level of improvement to change the negative situation in which the number of cases and deaths increased rapidly and 58 provinces turned into very high-risk groups. The increase in the number of daily cases and deaths was stopped at high numbers with the extension of restrictions on April 14, 2021 and a two-week partial closure. It is well known that the number of daily cases decreased to 7000 and deaths decreased to 120 by the end of May 2021 with the effect of some measures accompanying the radical decisions such as “suspending education at all levels” on April 26, 2021,

and “declaring a full closure until 05:00 on May 17, 2021” on April 29, 2021. In Figure 5, we focus on the situation when these measures are not taken or applied. The linear simulation obtained by the method of least squares show that the number of daily cases that occurred around 11,400 might reach 100,000 and the number of daily deaths, which were around 240, could exceed 500 in mid-May 2021.

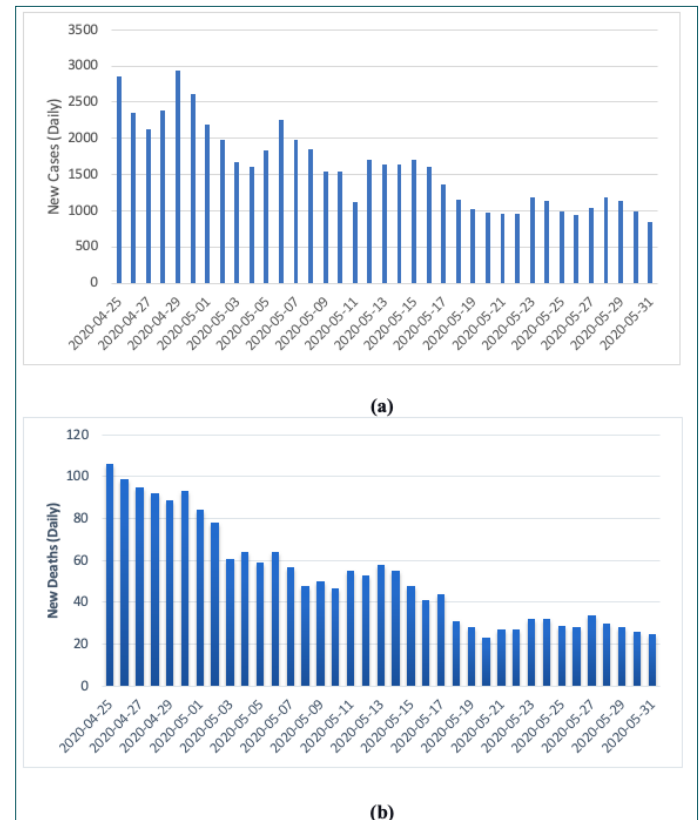


Figure 2. (a) May 4, 2020: Daily cases in the period of controlled social life (b) May 4, 2020: Daily deaths in the period of controlled social life

In addition to administrative measures, there are also some policies in the control of coronavirus: Vaccination began on April 2, 2021 and the number of vaccination exceeded 23 million doses by May 4, 2021. In Figure 6, we observe a stable process that continued until the end of June 2021 by taking revised precautions on May 16, 2021.

3.1.2. Effects of Vaccinations

In Figure 7, we observe high number of cases in mid-April 2021 and therefore the number of severe patients and the number of daily deaths reached its maximum value in this period. The growth rate of the number of vaccinations, together with the measures taken in May 2021, played an important role in the reduction of cases and deaths to relatively normal numbers at the end of May 2021. The fact that the priority of first dose or second dose vaccination was started for people who are at a high-risk of being affected by COVID-19 (i.e. over 65 years old or people with chronic disease) is an evidence that strengthens this assessment. The total number of vaccines administered in Turkey is given in Figure 7 as a column chart.

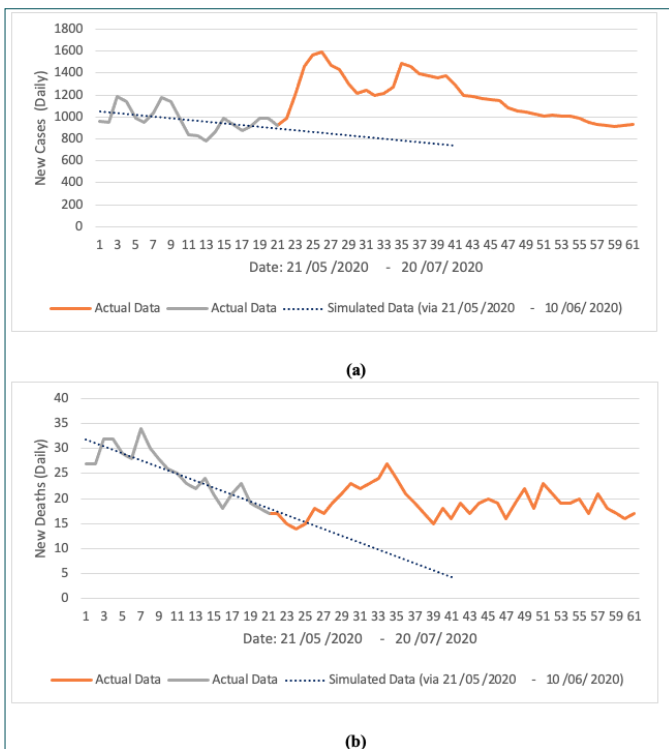


Figure 3. (a) The impact of the decisions (1 June 2020) on the number of daily cases. (b) The impact of the decisions (1 June 2020) on the number of daily deaths.

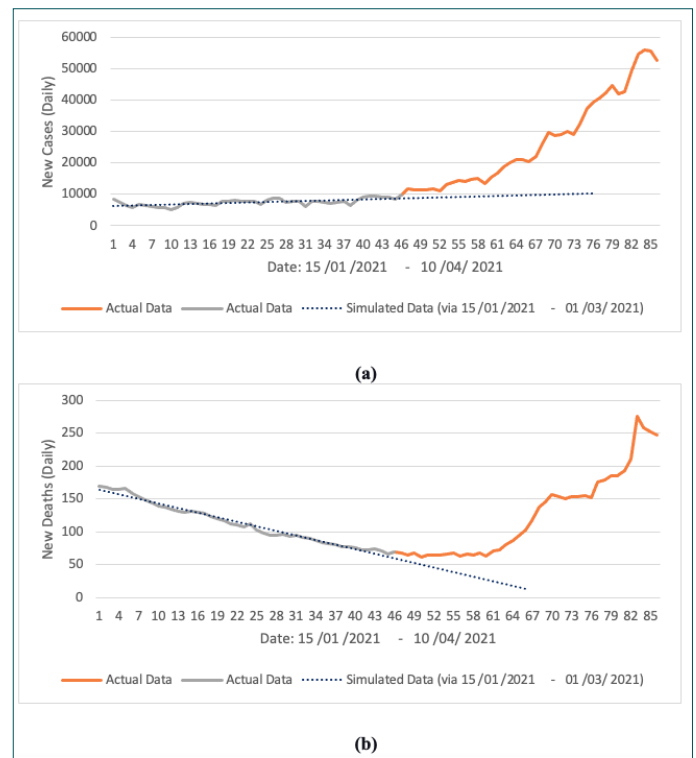


Figure 4. (a) Reflection of the decisions on 1 March 2021 and implementations on the number of daily cases. (b) Reflection of the decisions on 1 March 2021 and implementations on the number of daily deaths.



Figure 5. (a) The impact of the decisions taken on 14, 26, 29 April 2021 on the course of daily cases. (b) The impact of the decisions taken on 14, 26, 29 April 2021 on the number of daily deaths.

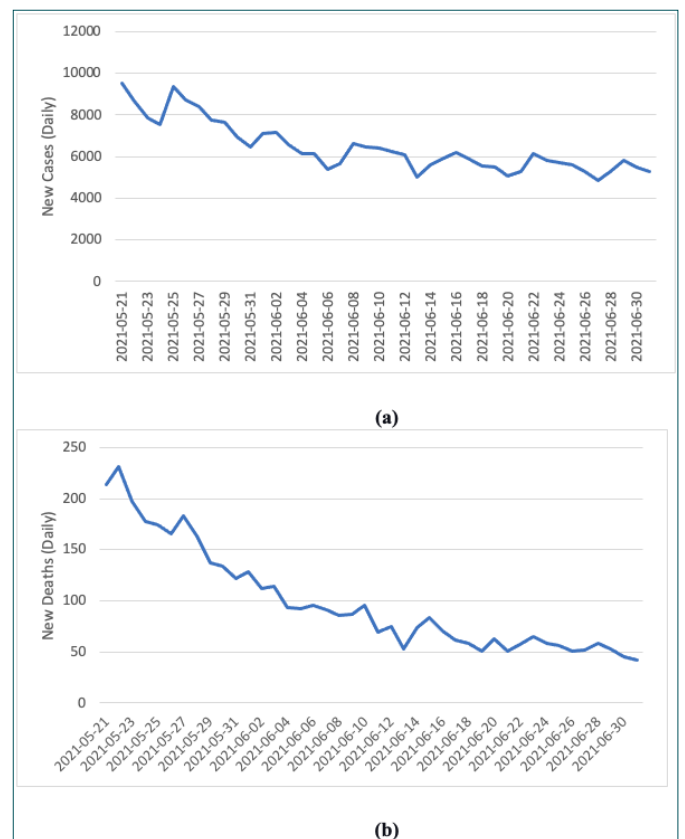


Figure 6. (a) The impact of decisions and implementations in May 2021 on daily case numbers. (b) The impact of decisions and implementations in May 2021 on the number of daily deaths

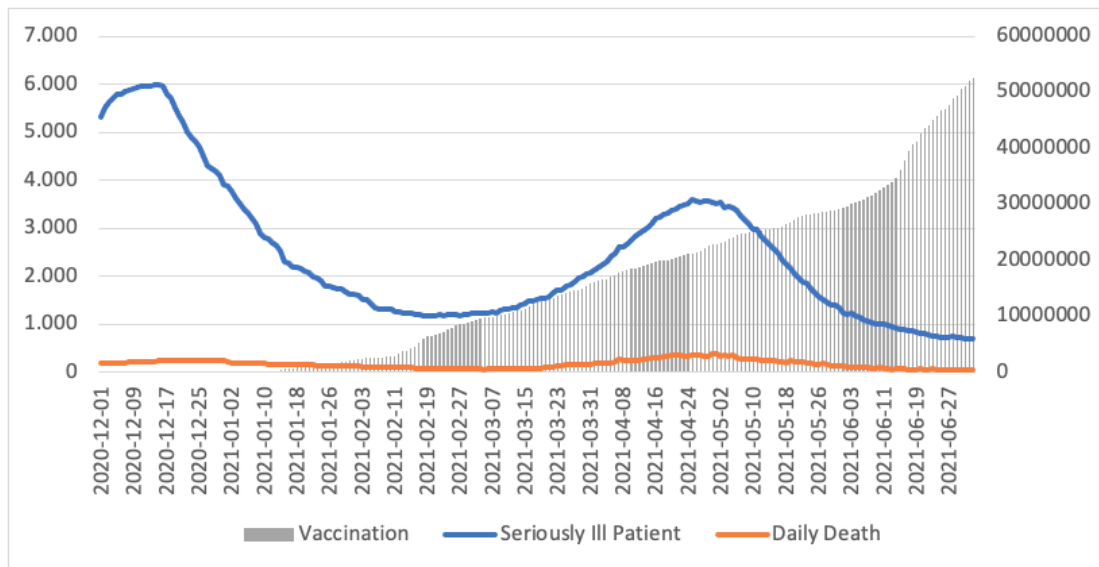


Figure 7. The effect of vaccination on the number of seriously ill patients and deaths

3.2. A Comparison of Some Developed Countries with Turkey

The situation in Turkey during the fight against COVID-19 is compared with the developed countries of Europe or neighboring countries such as Russia and Iran in terms of the indicators such as the rates of total number of cases and deaths.

3.2.1. Turkey's Position in Europe

We start with a comparison in terms of number of total case (Figure 8. (a)) and total death (Figure 8. (b)) rates for Turkey and developed countries of Europe such as Germany, England, France, and Italy. Here, the ratio of the number of cases (or deaths) to the population for each country is calculated as a percentage. Then, the weighted average of the four European countries was again obtained as a percentage and compared with the change in Turkey.

In Figure 8. (a), we observe that the total case rates in Turkey are lower than the average of the leading European countries, but the difference is small. The Figure 8. (b) shows that the average death rate in Europe is three times higher than in Turkey which can be seen as the most striking point of the process. These results reveal that we cannot draw parallels between the economic development levels of countries and the results received in the struggle with COVID-19. Republic of Turkey has one of the most disciplined and successful health policies in fighting against COVID 19 pandemic.

3.2.2. Turkey's Position in the Region

In Figure 9, the course of the pandemic in Turkey is compared with the leading countries in the region such as Russia and Iran in terms of the rates of total number of cases and deaths. Here, we consider the percentage of the total number of cases and deaths in each period and the ratio of the country's population as in previous section.

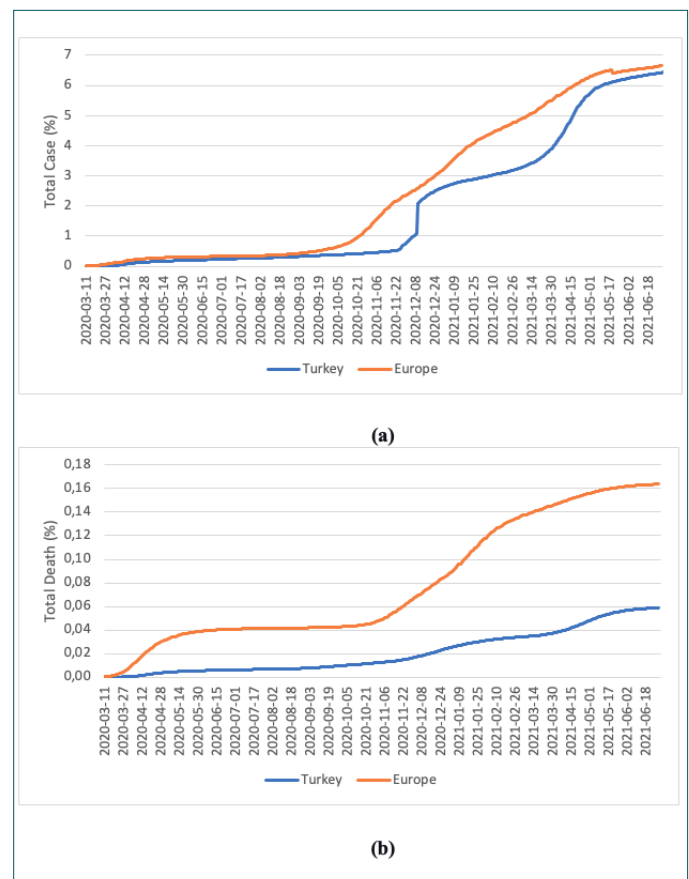


Figure 8. (a) Rates of total cases in Turkey and some developed European countries. (b) Rates of total deaths in Turkey and some developed European countries

In Figure 9. (a) we observe that the overall case rates in Turkey are higher than the neighboring countries such as Russia and Iran, especially after the addition of “asymptomatic cases” to the daily cases on 25 November 2020. However, the Figure 9. (b) shows that the death rates in Turkey are almost half of those in Iran and Russia. In the light of these data, it can be said that the implementations in Turkey give better results

than the leading countries in the region.

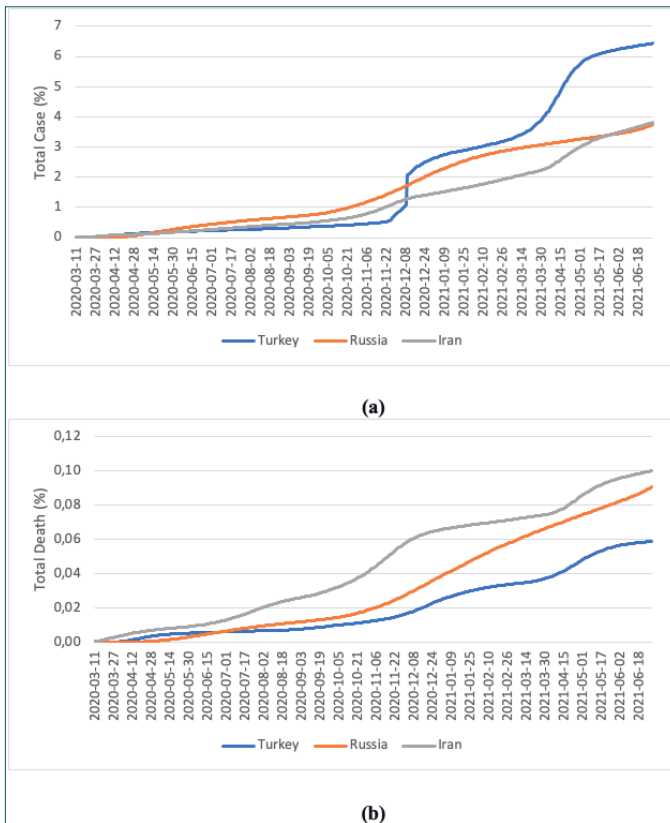


Figure 9. (a) Comparison of Turkey, Iran, and Russia in terms of total case rates. (b) Comparison of Turkey, Iran, and Russia by total death rate

4. Conclusion

In this study, the health policies implemented by Turkey in the fight against COVID-19 in the period of 10.03.2020-30.06.2021 are discussed. We observe that the policies adopted for the COVID-19 process are effective in reducing the number of cases and deaths. We also consider the scenario when the mentioned precautions were not taken.

It is clear that, it will not be realistic to interpret the COVID-19 pandemic process on the basis of one or two variables such as “number of case and death”. As almost every sector such as education, production, transportation, agriculture, tourism, service, supply, etc. are affected in the current process, decision makers have been taking into account many parameters to find an optimum solution. In this context, it can be said that the Ministry of Health has adopted the “occupation rate of intensive care capacities” as a red line and has adopted an attitude of increasing or decreasing the restrictions depending on this rate. In other words, a balanced policy was followed, centered on “providing a sustainable health service”. In this way, the opportunity was given to the continuation of economic activities under certain conditions.

Although Turkey’s overall situation in terms of total case rates in COVID-19 process is better than the average of some developed European countries, it is worse than the neighboring

countries such as Iran and Russia. However, mortality rates due to COVID-19 in Turkey are one-third of the European average and about a half of Iran and Russia. With a holistic approach that considers both the health policies in Table 1 and the figures which demonstrate the impacts of decisions, we can conclude that Turkey has a dynamic decision-making process for COVID-19. Moreover, the results obtained from these data points out that the health policy implemented in Turkey is quite successful and the provided health service is of high-quality.

Acknowledgment

The authors (A. Sendur and Z. Cakir) would like to acknowledge the support provided by Alanya Alaaddin Keykubat University, BAP Project No 2021-03-01-MAP01 for its funding a part of this research.

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Evaluation of Severe Fatigue and Related Factors in Ankylosing Spondylitis: a Cross-Sectional Study

Ankilozan Spondilitte Şiddetli Yorgunluk ve İlişkili Faktörlerin Değerlendirilmesi: Kesitsel Bir Çalışma

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Received: 02/10/2021

Accepted: 24/11/2021

Published Online: 02/12/2021

Abstract

Aim: Fatigue is an important symptom for patients with Ankylosing Spondylitis (AS). There is no accepted definitive scale to assess fatigue in AS. The purpose of the study was to measure fatigue by way of different scales in AS and find variables related to fatigue.

Method: The 77 AS patients and 61 controls were evaluated. Disease activity was evaluated by the BASDAI and ASDAS. Fatigue was evaluated with Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), Fatigue Severity Scale (FSS) and fatigue-related item of the BASDAI. Fatigue was compared in AS and controls.

Results: A total of 63.6% of patients had severe fatigue measured by fatigue-related item of BASDAI and 42% of patients had severe fatigue measured by FFS. The 26.2% of controls had severe fatigue. FSS scores were 3.9 ± 2 in AS patients and 2.3 ± 1.3 in controls ($p < 0.05$). There was strong correlation between FSS and fatigue item of BASDAI ($r = 0.763$, $p < 0.05$) similarly there was strong correlation FACIT-F score and fatigue-related item of BASDAI ($r = -0.736$, $p < 0.05$). FFS score was 2.38 ± 1.46 in inactive AS patients and 4.87 ± 1.68 in active patients ($p < 0.05$). Fatigue was statistically significant correlated with pain, disease activity, depression, functional capacity and anxiety in AS ($p < 0.05$). BASDAI was an independent predictor of severe fatigue in AS ($p < 0.05$).

Conclusion: Severe fatigue is more common in AS, especially those with the active disease. Disease activity, functional abilities, depression and anxiety were correlated with fatigue. One of the FSS, FACIT-F and fatigue-related item of BASDAI scores are sufficient to evaluate fatigue

Keywords: fatigue, ankylosing spondylitis,

Özet

Amaç: Yorgunluk, Ankilozan spondilit (AS) hastalarında önemli bir semptomdur. AS'de yorgunluğu değerlendirmek için kabul edilmiş kesin bir ölçek yoktur. Çalışmanın amacı, AS'de yorgunluğu farklı ölçeklerle ölçmek ve yorgunluk ile ilgili değişkenleri bulmaktır.

Yöntem: 77 AS hastası ve 61 kontrol değerlendirildi. Hastalık aktivitesi BASDAI ve ASDAS ile değerlendirildi. Yorgunluk Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), Fatigue Severity Scale (FSS) ve BASDAI'nin yorgunlukla ilişkili maddesi ile değerlendirildi. Yorgunluk AS ve kontrollerde karşılaştırıldı. Yorgunluk ile hastalıkla ilişkili parametrelerin korelasyonu değerlendirildi.

Bulgular: Hastaların %63.6'sında BASDAI'nin yorgunlukla ilgili maddesi ile ölçülen ve %42'sinde FFS ile ölçülen şiddetli yorgunluk vardı. Sağlıklı kontrollerin %26.2'sinde şiddetli yorgunluk vardı. FSS skoru AS hastalarında 3.9 ± 2 , kontrollerde 2.3 ± 1.3 idi ($p < 0.05$). FSS ile BASDAI'nin yorgunluk maddesi arasında güçlü bir korelasyon vardı ($r = 0.763$, $p < 0.05$), benzer şekilde FACIT-F ile BASDAI'nin yorgunluk maddesi arasında da güçlü bir korelasyon vardı ($r = -0.736$, $p < 0.05$). İnaktif AS hastalarında FFS skoru 2.38 ± 1.46 , aktif hastalarda 4.87 ± 1.68 idi ($p < 0.05$). Yorgunluk, AS'de ağrı, hastalık aktivitesi, depresyon, fonksiyonel kapasite ve anksiyete ile istatistiksel olarak anlamlı korelasyon vardı ($p < 0.05$). BASDAI, AS hastalarında şiddetli yorgunluğun bağımsız ön gördürücüsüdür ($p < 0.05$).

Sonuç: AS'de, özellikle aktif hastalığı olanlarda şiddetli yorgunluk daha yaygındır. Hastalık aktivitesi, fonksiyonel durum, depresyon, ağrı ve anksiyete yorgunluk ile ilişkilidir. BASDAI skorunun yorgunlukla ilgili maddesi, FSS, FACIT-F'den biri yorgunluğu değerlendirmek için yeterlidir.

Anahtar kelimeler: yorgunluk, ankilozan spondilit

Cite this article: Ugur S. Evaluation of Severe Fatigue in Ankylosing Spondylitis a cross-sectional study. Turk J Health S. 2021;2(3):pp.49-53.



Introduction

Ankylosing Spondylitis (AS) is a chronic inflammatory rheumatic disease (1). Fatigue has been reported as one of the most common symptoms of AS, in addition to pain and stiffness (2). Fatigue is described as a lack of energy and exhaustion following an activity (3,4). Fatigue has been reported in various rheumatic diseases (5,6), and some previous studies have reported a frequency of fatigue at 53-63% in patients with AS (7,8). Fatigue is an important symptom for AS patients because it affects physical function, daily and social activities and causes morbidity (9), it has been reported as one of the main factors causing work instability in AS (10). Although one of the most important complaints reported by AS patients is fatigue, sufficient attention is not granted in the routine follow-ups and there is no definitively accepted scale to evaluate fatigue in patients with AS to date. In number of studies, fatigue in patients with AS has been evaluated solely using the question regarding fatigue in Bath ankylosing spondylitis disease activity index (BASDAI) (8,9,11). The purpose of the study was to assess levels of fatigue in AS and healthy controls by way of three different fatigue scales and to uncover variables related to severe fatigue in AS.

Material and Methods

In this cross-sectional study, 77 patients diagnosed with AS according to the Modified New York criteria (12) and 61 age and gender matched healthy hospital workers, were included. The G.POWER.3.1 program was used for power calculation. Subjects who had another an inflammatory rheumatic disease, fibromyalgia (FM), Diabetes mellitus, hyperlipidemia, hypertension, hypothyroidism, osteomalacia and psychiatric disorders, were excluded. The Visual Analogue Scale (VAS) was used to assess pain (13).

Disease activity was evaluated by using the BASDAI and the Ankylosing spondylitis disease activity score (ASDAS). ASDAS evaluated back pain, morning stiffness, joint involvement, patient general assessment in combination with laboratory parameters. ASDAS <1.3 indicates an inactive disease, ASDAS <2.1 indicates low disease activity, 2.1<ASDAS ≤ 3.1 indicates high disease activity and >3.1 indicates very high activity (14,15). BASDAI ≥ 4 is defined as an active disease (11).

Functionality was appraised with the Bath Ankylosing Spondylitis Functional Index (BASFI) (16). Quality of life was assessed with the Ankylosing Spondylitis Quality of Life (ASQoL) Scale (17). Depression and anxiety were evaluated by the Beck depression and Beck anxiety inventory respectively, higher scores showing more severe depression and anxiety (18,19).

Fatigue

Fatigue was evaluated using the Functional Assessment of

Chronic Illness Therapy (FACIT) -Fatigue Scale (FACIT-F) and Fatigue Severity Scale (FSS) and fatigue-related item of the BASDAI (first question of the BASDAI). The FSS consists of 9 items that evaluate social, cognitive and physical effects of fatigue. The scoring is accomplished by calculating the average of items. A value of 3 or higher indicates severe fatigue (20). Individuals with an FSS ≥ 3 or fatigue-related item of BASDAI ≥ 5 were classified as having severe fatigue. FACIT-F scale consists of 13-items which evaluate the effects of tiredness, weakness and lack of energy, daily functioning and sleep. Higher scores indicate higher functional status and less fatigue (21).

Permission for the study was obtained from the XXXX University Faculty of Medicine Ethics Committee, decision number 05-04 on 10/03/2021. Written informed consent was obtained from all participants.

The IBM SPSS version 22.0 was used for analysis and t-test was used to compare variables. Correlations between fatigue and clinical parameters were evaluated using Spearman correlation test. Binary logistic regression analysis was applied using the absence or presence of severe fatigue (according to the cutoff value of 3 for FSS and cut off value of 5 for the fatigue-related item of BASDAI) as the dependent variable to state predictors of severe fatigue.

Results

A total of 77 AS patients and 61 healthy controls were evaluated. The features of subjects are given in Table 1. The mean BASDAI and ASDAS were 4.5±2.12 and 2.91±1.05 respectively. Some 61% of patients with AS had an active disease according to the BASDAI (BASDAI ≥4). Otherwise, 2%, 22.1%, 36.4% and 39% of patients had inactive, low activity, high activity and very high disease activity respectively, according to ASDAS. There was 18.2% of patients who were receiving a sulfasalazine treatment, 18.2% were on biologics and 61% of were on nonsteroidal anti inflammatory drugs (NSAIDs).

The 63.6% of AS patients had severe fatigue as measured by fatigue related item of BASDAI and 42 % of AS patients had severe fatigue as measured by FFS. According to FFS 26.2% of controls had severe fatigue. According to fatigue item of BASDAI 36.1% of controls had severe fatigue. Severe fatigue was more common in AS patients (p<0.05).

FSS was 3.9±2 in AS patients and 2.3±1.3 in controls (p<0.05). The FFS score was 2.38±1.46 in inactive AS patients (BASDAI <4) and 4.87±1.68 in active AS patients (BASDAI ≥ 4). The FACIT-F score was lower in AS than in healthy controls (p<0.05). The FACIT-F score was 36.03±7.72 in inactive AS patients and 23.91±9.98 in active AS patients. Fatigue was higher in active disease compared to inactive disease (p<0.05).

Fatigue in AS patients was statistically significant correlated

with, pain, disease activity, functional capacity, depression and anxiety ($p<0.05$) (Table 2). Differences between fatigue groups are shown in Table 3. The FSS was strongly correlated with fatigue related item of BASDAI ($r=0.763$, $p<0.05$) and similarly, there was a strong correlation with the FACIT-F score and fatigue-related item from the BASDAI ($r=-0.736$, $p<0.05$).

Table 1. Characteristics of the patients and controls

	AS patients (n=77)	Healthy controls (n=61)	P value
Age	38.31±10.61	38.21±7.34	$p>0.05$
Gender(naun,percent)			
•Female	26 (33.8%)	19 (31.8%)	$p>0.05$
•Male	51 (66.2%)	42 (68.9%)	$p>0.05$
Marital status			
•Married	59 (76.6%)	49 (80.3%)	$p>0.05$
•Non married	18 (23.4%)	12 (19.7%)	$p>0.05$
Employment			
•Employed	51 (66.2%)	58 (95.1%)	$p<0.05$
•Unemployed	26 (33.8%)	3 (4.9%)	$p<0.05$
Smoking			
•Smoking	28 (36.6%)	12 (19.6%)	
•No smoking	49 (63.4%)	49 (80.32%)	
Disease duration (year)	9.7±8.13	-	
Fatigue item of BASDAI (range: 0–10)	5.23±2.49	3.82±1.99	$p<0.05$
FACIT-F	28.63±10.88	36.31±8.73	$p<0.05$
FSS	3.9±2	2.3±1.3	$p<0.05$
Beck Depression score	12.38±8.68	6.06±8.07	$p<0.05$
Beck Anxiety score	14.68±10.66	6.32±6.75	$p<0.05$
BASDAI (range: 0–10)	4.5±2.12	-	
ASDAS	2.91±1.05	-	
BASFI (range: 0–10)	3.55±2.86	-	
C-reaktif protein (mg/dL)	0.95±1.76	-	

Binary logistic regression demonstrated that BASDAI is an independent predictor of severe fatigue in AS patients (according to BASDAI fatigue item ≥ 5 , OR: 2.836, $p<0.05$) (according to FSS ≥ 3 : OR:3.453 $p<0.05$) (Table 4,5).

Discussion

This study was performed to evaluate the fatigue in AS patients and healthy controls using three different scales and to evaluated the relation between disease-related parameters and fatigue in AS. Fatigue was found to be more common in AS patients. In previous studies, fatigue has been generally assessed with the fatigue related-item of the BASDAI (8,9). Therefore this study differentiates itself from others that have evaluated fatigue in patients with AS, because fatigue was assessed with three different scores. Indeed fatigue was evaluated by FSS and FACIT-F as well as the fatigue-related item of BASDAI. The 63.3% of AS patients had severe fatigue defined as per the BASDAI fatigue score ≥ 5 and 54.5% of AS

patients were found the have severe fatigue defined as FSS ≥ 3 . Patients with AS had lower FACIT-F scores compared to healthy controls and also, active AS patients had lower scores than inactive AS patients. This results supported that healthy controls and non active AS patients had less fatigue. There was a the strong correlation between FSS, FACIT-F and fatigue-related item of BASDAI. This result suggests that using one of these scores in future studies may be sufficient to evaluate fatigue in patients with AS.

Table 2. Correlation analysis results of AS patients.

	FSS	FACIT-F	fatigue item of BASDAI
BASDAI	$r= 0.750$ $p<0.05$	$r= -0.735$ $p<0.05$	$r= 0.785$ $p<0.05$
ASDAS	$r=0.400$ $p<0.05$	$r= 0.388$ $p<0.05$	$r= 0.478$ $p<0.05$
BASFI	$r= 0.590$ $p<0.05$	$r= 0.581$ $p<0.05$	$r= 0.533$ $p<0.05$
ASQUEL	$r= 0.642$ $p<0.05$	$r= - 0.600$ $p<0.05$	$r= 0.569$ $p<0.05$
BECK Depression	$r= 0.475$ $p<0.05$	$r= -0.548$ $p<0.05$	$r= 0.349$ $p<0.05$
BECK Anxiety	$r= 0.528$ $p<0.05$	$r= - 0.704$ $p<0.05$	$r= 0.472$ $p<0.05$
VAS ağrı	$r= 0.353$ $p<0.05$	$r= 0.420$ $p<0.05$	$r= 0.385$ $p<0.05$
CRP	$r= 0.004$ $p>0.05$	$r=0.180$ $p>0.05$	$r= 0.08$ $p>0.05$

Fatigue has been reported to be related with disease activity in studies evaluating BASDAI as the disease activity score (8). In most studies related with AS, disease activity was evaluated with only BASDAI. In this study, disease activity was assessed with using both BASDAI and ASDAS and it was observed that fatigue was strongly correlated with both activity scores. AS patients were grouped as active and inactive disease according to BASDAI. The majority of patients had active disease and it was also found that active AS patients had more severe fatigue. It was found that BASDAI predicted severe fatigue in AS patients evaluated by the FSS scale and the BASDAI fatigue-related item. Consistently with these results Zhou et al. reported that BASDAI was an independent predictive factor for fatigue assessment by FSS (4).

Table 3: Differences between fatigue group with respect to the disease specific measures.

	BASDAI fatigue item ≥ 5	BASDAI fatigue item < 5	p	FSS ≥ 3	FSS < 3	P value
Fatigue item of BASDAI	6.77±1.59	2.53±1.07	$p<0.05$	6.76±1.89	3.4±1.89	$p<0.05$
BASDAI	5.55±1.77	2.89±1.54	$p<0.05$	5.86±1.66	3.04±1.5	$p<0.05$
ASDAS	3.16±0.99	2.47±1.01	$p<0.05$	3.32±0.8	2.4±1.08	$p<0.05$
BASFI	4.46±2.96	1.9±1.72	$p<0.05$	5.01±2.82	1.75±1.63	$p<0.05$
ASQoL	10.02±4.44	5.28±4.55	$p<0.05$	11.04±3.9	5±4.07	$p<0.05$
Beck depression	14.35±7.88	9±9.07	$p<0.05$	15.87±8.9	8.2±6.3	$p<0.05$
Beck anxiety	17.55±11.25	9.67±7.34	$p<0.05$	19.09±11.3	9.4±6.8	$p<0.05$
FACIT	23.42±9.33	37.7±6.56	$p<0.05$	21.76±9.08	36.8±6.05	$p<0.05$
FSS	4.92±1.7	2.13±0.97	$p<0.05$	5.48±1.22	2.01±0.6	$p<0.05$

FM has been commonly reported in patients with AS. The co-

existence of AS and FM leads to confusion in patient-reported results of disease on account of overlapping symptoms (22). Therefore in this study, to avoid confusion, patients had fibromyalgia were not included.

Table 4: Factors related with the presence of severe fatigue (FSS ≥ 5) in AS patients by binary logistic regression analysis.

	β	S.E	Wald	Sig	Exp (B)	95 % CI
Age	0.046	0.054	0.729	0.393	1.047	0.942-1.165
Disease duration	-0.010	0.072	0.018	0.893	0.990	0.860-1.140
VAS pain	-0.188	0.201	0.873	0.350	0.829	0.559-1.229
BASDAI	1.239	0.533	5.404	0.02	3.453	1.215-9.817
ASDAS	-0.668	0.825	0.655	0.418	0.513	0.102-2.583
BASFI	0.288	0.309	0.866	0.352	1.334	0.727-2.445
Beck Anxiety	-0.015	0.067	0.053	0.818	0.985	0.864-1.122
Beck depression	0.146	0.068	4.632	0.03	1.157	1.013-1.321
ASQoL	0.059	0.136	0.188	0.665	1.061	0.813-1.383
CRP	0.402	0.379	1.124	0.289	1.495	0.711-3.144

Table 5: Factors related with the presence of severe fatigue (BASDAI related item ≥ 5) in AS patients by binary logistic regression analysis

	β	S.E	Wald	Sig	Exp (B)	95 % CI
Age	-0.025	0.029	0.701	0.403	1.025	0.968-1.085
Disease duration	-0.018	0.037	0.247	0.619	0.982	0.913-1.056
VAS pain	0.175	0.095	3.396	0.06	1.191	0.989-1.434
BASDAI	1.042	0.456	5.230	0.022	2.836	1.161-6.928
ASDAS	-0.506	0.482	1.102	0.294	0.603	0.235-1.550
BASFI	0.071	0.271	0.069	0.793	1.074	0.631-1.828
Beck Anxiety	-0.068	0.078	0.741	0.389	0.935	0.801-1.090
Beck depression	-0.025	0.060	0.173	0.678	0.975	0.867-1.097
ASQoL	-0.173	0.169	1.042	0.307	0.841	0.604-1.172
CRP	-0.005	0.135	0.001	0.970	0.995	0.763-1.297

In the present study, functional disability was found to be related with fatigue and AS patients with severe fatigue had worse functionality. Turan et al. found similar result (23). The relationship between fatigue and acute phase reactants is still unclear. Dagwnrud et al. reported that there was no

relationship between fatigue and CRP (24). In concordance with this result there was no relation between fatigue and ESR and CRP in this study.

Dernis-Labous et al. showed that nonsteroidal anti-inflammatory drug therapy did not have a significant effect on reducing fatigue (9). Bedaiwi et al. found significant but weak relation between CRP and fatigue. In their study fatigue persisted in majority of patients, although there was a significant decrease in FSS by using TNFi therapy (25). Although most of the AS patients used NSAIDs, the frequency of severe fatigue was quite high in this study. On the other hand, CRP was not found to be an independent predictor of severe fatigue. This result supports that the role of inflammation is still unclear in severe fatigue and there is a need for studies explaining the relation between inflammation and fatigue.

Quality of life is significantly reduced in AS (26). In our study patients with severe fatigue had a lower quality of life and the frequency of depression was higher in AS. There was a significant relationship between fatigue and depression. Aissaoui et al. reported that compared with non-fatigue patients, fatigue patients had more significant anxiety and depression (27).

In conclusion, this study had shown that severe fatigue was more common in AS patients, in particular those with active disease. Disease activity, functional abilities, depression, pain and anxiety were significantly correlated with fatigue in patients with AS. BASDAI was the main independent factor that predicted fatigue. The effect of inflammation is still unclear in severe fatigue and studies evaluating the relationship between inflammation and fatigue in patient with AS are needed. One of FSS, FACIT-F and fatigue-related item of BASDAI scores is sufficient to evaluate fatigue.

Financial support: There is no source of financing.

Conflict of interest: There is no conflict of interest.

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Normalization of Increased Upper Trapezius Muscle Activity with EMG Biofeedback Training in a Patient with Surgically Treated Fragmented Proximal Humerus Fracture: One-Year Follow-up Results of the Case

Proksimal Humerus Kırığının Cerrahi Olarak Tedavi Edildiği Hastada Artmış Üst Trapezius Kas Aktivitesinin EMG Biofeedback Eğitimi ile Normalize Edilmesi: Olgunun Bir Yıllık Takip Sonuçları

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Received: 03/06/2021

Accepted: 11/08/2021

Published Online: 02/12/2021

Abstract

Aim: To evaluate the one-year results of the effects of electromyography (EMG) biofeedback training included in the traditional rehabilitation program on symptoms, upper trapezius muscle activity, functional status, and quality of life in a patient with surgically treated fragmented proximal humerus fracture.

Method: The patient's pain severity (Visual Analogue Scale), range of motion (Universal goniometer), grip strength (Jamar Hydraulic Hand Dynamometer), scapular position (Lateral Scapular Slide Test), fear of movement (Tampa Kinesiophobia Scale), the functional status of the upper extremity (Disabilities of the Arm, Shoulder, and Hand Questionnaire), quality of life (SF-36 Scale), upper trapezius muscle activity (surface EMG) were evaluated before and after the treatment, and at one-year follow-up. The EMG biofeedback training, which was included in the traditional rehabilitation program, was applied for eight weeks to normalize the increased upper trapezius muscle activity.

Results: It was found that pain severity and fear of movement were decreased, range of motion, grip strength, functional status of the upper extremity, and quality of life were increased after the treatment and at one-year follow-up. Also, the increased upper trapezius muscle activity was normalized and the asymmetry in the scapula position was decreased.

Conclusion: A well-planned rehabilitation program, including EMG biofeedback training, can reduce the symptoms, improve the functional status and the quality of life in a patient with surgically treated fragmented proximal humerus fracture.

Keywords: Humeral head, Fracture, EMG biofeedback, Upper trapezius, Rehabilitation

Özet

Amaç: Parçalı proksimal humerus kırığının cerrahi olarak tedavi edildiği hastada geleneksel rehabilitasyon programına dahil edilen elektromiyografi (EMG) biofeedback eğitiminin semptomlar, üst trapezius kas aktivitesi, fonksiyonel durum ve yaşam kalitesi üzerine bir yıllık sonuçlarını değerlendirmektir.

Yöntem: Hastanın ağrı şiddeti (Görsel Analog Skala), eklem hareket açıklığı (Universal gonyometre), kavrama kuvveti (Jamar Hidrolik El Dinamometresi), skapular pozisyon (Lateral Skapular Slide Test), hareket korkusu (Tampa Kinezyofobi Skalası), üst ekstremitte fonksiyonel durumu (Kol, Omuz ve El Sorunları Anketi), yaşam kalitesi (SF-36 Ölçeği), üst trapezius kası aktivitesi (yüzeysel EMG) tedavi öncesi, tedavi sonrası ve bir yıllık takipte değerlendirildi. Artmış üst trapezius kas aktivitesini normalize etmek için geleneksel rehabilitasyon programına dahil edilen EMG biofeedback eğitimi sekiz hafta boyunca uygulandı.

Bulgular: Tedavi sonrasında ve bir yıllık takipte ağrı şiddeti ve hareket korkusunun azaldığı, eklem hareket açıklığı, kavrama kuvveti, üst ekstremitte fonksiyonel durumu ve yaşam kalitesinin arttığı bulundu. Ayrıca, artmış üst trapezius kas aktivitesinin normale döndüğü ve skapula pozisyonundaki asimetrisinin azaldığı görüldü.

Sonuç: Parçalı proksimal humerus kırığının cerrahi olarak tedavi edildiği hastada, EMG biofeedback eğitimi içeren iyi planlanmış bir rehabilitasyon programı semptomları azaltabilir, fonksiyonel durumu ve yaşam kalitesini iyileştirebilir.

Anahtar Kelimeler: Humerus başı, Kırık, EMG biofeedback, Üst trapezius, Rehabilitasyon

Cite this article: Yıldız NT., Kocaman H., Erden Z. Normalization of Increased Upper Trapezius Muscle Activity with EMG Biofeedback Training in a Patient with Surgically Treated Fragmented Proximal Humerus Fracture: One-Year Follow-up Results of the Case. Turk J Health S. 2021;2(3):pp.54-58.

Introduction

Proximal humeral fractures (PHF) can range from non-displaced fractures to serious fragmented head and neck fractures (1). Various treatment methods are used in PHK, including conservative treatment, Open Reduction and Internal Fixation (ORIF), and hemiarthroplasty, depending on the condition of the fracture and the patient (2). Following the surgical treatment of PHK with ORIF, upper trapezius (UT) EMG activity increases to compensate for the developing deltoid muscle inhibition. As a result, the normal kinematics of the scapula deteriorate and scapular dyskinesia occurs. Scapular dyskinesia leads to the shoulder complex working inefficiently and increases energy consumption in activities of daily living. Also, fatigue and pain occur in the muscles around the scapula and shoulder. Dynamic control of the shoulder complex is considered essential for the efficient functioning of the upper limb. The harmony of the upper and lower fibers of the trapezius muscle with the serratus anterior muscle is important for the stabilization of the scapula and to maintain the coordinated movement between the scapula and the humerus (3,4). In cases of scapula and shoulder problems, increased activity of the UT muscle compared to the middle and lower trapezius muscle is a common clinical condition. This condition first deteriorates the normal kinematics of the scapula, then causes muscular imbalance by changing the length-tension relationship between the scapula and shoulder muscles (5).

After surgical treatment of PHK with ORIF, patients could experience problems such as pain, stiffness, and loss of function that decrease the quality of life. However, it has been reported that an effective rehabilitation program applied after surgery can minimize these problems and increase the patient's functional status and quality of life (2). One of the main objectives in the rehabilitation of shoulder-related injuries is re-establishing appropriate scapular positioning during movement, which is achieved through re-training the scapular stabilizer muscles (6).

Surface electromyography (EMG) indicates the sum of motor unit action potentials detected by surface electrodes in muscles. EMG is a non-invasive evaluation method that provides information about muscles. EMG biofeedback training is used as a treatment method to improve the neuromuscular control of the affected muscles in different problems (7). It also ensures patients a better sense of the different muscle activation patterns involved in the movement of the shoulder complex. EMG biofeedback training has been used in rehabilitation programs for patients with shoulder pain in clinical settings (6).

To our knowledge, there was no study in the literature in which increased UT muscle activation was normalized

using EMG biofeedback training in patients with surgically treated fragmented PHF. In this study, it was thought that the rehabilitation program, which includes the normalization of increased UT EMG activity with EMG biofeedback training method in addition to strengthening the deltoid, serratus anterior, and lower trapezius muscles could increase the functional level and quality of life of the patient. Therefore, the purpose of this study was to examine the one-year follow-up results of the effects of an eight-week rehabilitation program, including the normalization of increased UT EMG activity with EMG biofeedback training in addition to a traditional rehabilitation program in a patient with a surgically treated (ORIF) fragmented PHF.

Case Presentation

A 63-year-old male patient occurred left fragmented PHF after a traffic accident and was surgically treated with ORIF (Figure 1). The patient, whose shoulder was immobilized for four weeks after surgery, then performed the exercises given to him at home for three weeks. Since the symptoms of pain and limitation of movement in his shoulder do not decrease, the patient applied to our clinic. This study was conducted by the Faculty of Physiotherapy and Rehabilitation, Hacettepe University, Ankara, Turkey.



Figure 1. Left side fragmented PHF (after ORIF)

After the verbal and written consent was obtained, the patient was included in an eight-week rehabilitation program that consists of evaluation and treatment methods. The pain severity, ROM, grip strength, scapular position, fear of movement, upper extremity functional status, quality of life, and UT EMG activity were evaluated before and after the rehabilitation program, and at the one-year follow-up. The severity of pain in the left shoulder during rest and activity, and at night was evaluated using the visual analog scale (VAS) (8).

The shoulder flexion, extension, external rotation, and internal rotation ROMs were measured with a Universal goniometer in the supine position. The grip strength was measured by Jamar Hydraulic Hand Dynamometer in an upright sitting position with arms adjacent to the body and elbow at 90° flexion position. The average of three measurements for the right and the left sides were recorded in kilograms (kg). The Lateral Scapular Slide Test (LSST), which is reported to be a reliable method for evaluating the scapular position, was used. The distance of the infero-medial angle of the scapula to the thoracic spine in three different positions (Position 1: arms adjacent to the body, Position 2: hands are on the iliac crests, Position 3: arms in 90° abduction) while standing was measured and recorded in cm. The asymmetry between the left and right scapular positions was examined (9).

The fear of movement with the Tampa Kinesiophobia Scale (TKS) (10), the functional status of the upper extremity with the Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) (11), and quality of life with the SF-36 scale (12) were evaluated. The patient was over-activating the UT muscle during left shoulder flexion and abduction movements. It was observed that with palpation UT muscle tonus at rest and during shoulder flexion and abduction was greater than the right side. EMG activity of the left and right UT muscles was evaluated in three different positions (Measurement 1: hands on the legs and the arms adjacent to the body (in resting position), Measurement 2: at 90° shoulder flexion position, Measurement 3: at 90° shoulder abduction position) while sitting, using the “sEMG mode” of the “Chattanooga Group a Division of Encore Medical” combined electrical stimulation device. While evaluating the EMG activity of the UT, two active electrodes (recording electrodes) (Dura-stick II 1.25 inch) were placed on the surface of the “UT” muscle at 2 cm intervals and parallel to the muscle fibers. A reference electrode (passive electrode) was placed on the medial edge of the scapula (Figure 2/A) (6). The values of EMG activity at three positions were recorded in microvolts (μV). It was found that the EMG activity of the left UT muscle was significantly increased in all three positions compared to the right side (Table 1). EMG biofeedback training using the combined electrical stimulation device’s “sEMG mode” was performed for three sessions per week for eight weeks in addition to a traditional rehabilitation program to normalize the increased UT EMG activity. During the EMG biofeedback training, the patient performed two exercises, while looking at the projected EMG biofeedback column graph on the screen to see the EMG activity of UT muscle while the exercises were being performed. EMG activity of the left UT was monitored by the patient during the 90° shoulder flexion and abduction exercises. This ensured a real-time visualization of the EMG activity, while the patient performs the exercises. Through this, the patient was able to control and isolate the UT, during

the two exercises. In order to achieve a good training effect, the patient was asked to actively reduce upper trapezius EMG activity shown on the screen (6). These two exercises were progressed from one set to three sets and from 10 repetitions to 15 repetitions from active movement to resistance exercise (with Thera-band® elastic band) throughout the rehabilitation program. Also, each repetition was held for five seconds (Figure 2/B).

Transcutaneous Electrical Nerve Stimulation therapy was used for pain. Exercises were initiated with passive and active assistance to increase the ROMs, and to strengthen the deltoid, rotator cuff, lower trapezius, and serratus anterior muscles, and progressed as active and resistant exercises according to the patient’s tolerance.

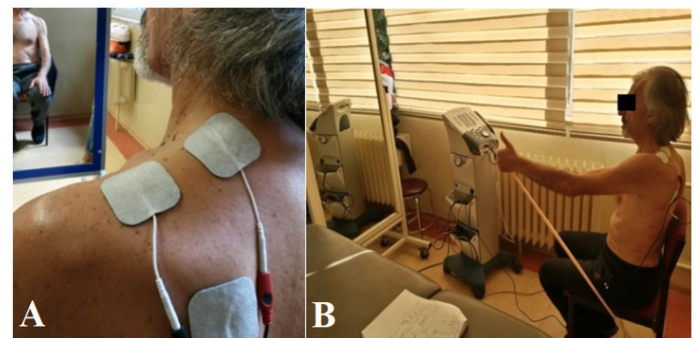


Figure 2. A: Location of surface EMG electrodes, B: EMG biofeedback training during the 90° shoulder flexion exercise

It was observed that the increased upper trapezius EMG activity of the effected side decreased after the treatment program and had similar values with the non-effected side at the one-year follow-up (Table 1).

Table 1. Changes in upper trapezius muscles EMG activity

	Left UT EMG activity			Right UT EMG activity
	BT	AT	1-YF	
Measurement 1 (μV)	175-184	25-30	23-29	18-23
Measurement 2 (μV)	213-220	32-36	27-31	22-29
Measurement 3 (μV)	230-235	42-48	30-36	24-30

BT: Before treatment, AT: After treatment, 1-YF: One-year follow-up, UT: Upper trapezius, μV : Microvolt, Measurement 1: Hands on the legs and the arms adjacent to the body (in resting position), Measurement 2: at 90° shoulder flexion position, Measurement 3: at 90° shoulder abduction position

While the pain severity during rest and activity, and at night were 5, 7, and 7, respectively, according to VAS before the treatment, the patient had no pain after the treatment and at the one-year follow-up. Considerable increases were obtained in all active ROM values of the left shoulder, and left-hand grip strength after treatment and at one-year follow-up (Table 2) (Figure 3).

Table 2. Changes in ROM and handgrip strength

		Left (effected side)			Right
		BT	AT	1-YF	
Shoulder ROM (°)	Flexion	52	160	170	172
	Abduction	48	163	175	180
	External rotation	18	66	70	76
	Internal rotation	15	57	60	72
Hand grip strength (kg)		18.3	39.6	40.2	43

BT: Before treatment, AT: After treatment, 1-YF: One-year follow-up, ROM: Range of motion



Figure 3. Left and right shoulder ROMs at one-year follow-up

It was observed that the asymmetry in the position of the left scapula decreased according to the LSST after treatment and at the one-year follow-up (Table 3).

Table 3. Changes in scapular positions according to LSST

	Left Scapula			Right Scapula
	BT	AT	1-YF	
Position 1 (cm)	8	9	9.5	10
Position 2 (cm)	10	11	11.5	12
Position 3 (cm)	11	11.5	12	12.5

BT: Before treatment, AT: After treatment, 1-YF: One-year follow-up, Position 1: arms adjacent to the body, Position 2: hands are on the iliac crests, Position 3: arms in 90° abduction

After treatment and at one-year follow-up, there was a decrease in the TKS and DASH scores, and an increase in the scores of the PCS and MCS subsections of the SF-36 scale (Table 4).

Table 4. Changes in TKS, DASH, and SF-36 scale scores

		BT	AT	1-YF
TKS		39	22	20
DASH		80.17	25	6.7
SF-36	PCS	25	50	100
	MCS	22	52	100

BT: Before treatment, AT: After treatment, 1-YF: One-year follow-up, TKS: Tampa Kinesiophobia Scale, DASH: Disabilities of the Arm, Shoulder, and Hand Questionnaire, PCS: Physical Component Score, MCS: Mental Component Score

Discussion

In the present study, it was found that pain, fear of movement, and asymmetry in the scapula position were decreased, and

ROM, upper extremity functional status, and quality of life were increased in patient with surgically treated fragmented PHF after the eight-week rehabilitation program, and at the one-year follow-up.

The normal three-dimensional movement of the scapula during shoulder elevation is critical in maintaining the normal glenohumeral rhythm, preserving the subacromial space, and maximizing the length-tension relationship of the muscles. It has been reported that excessive activation of UT leads to abnormal scapular movement and deteriorates the glenohumeral rhythm (13). In patients with shoulder problems, increased UT and reduced serratus anterior EMG activity cause an imbalance in force production of these muscles, the excessive elevation of the shoulder, and the inability of the upward and posterior tilt movements of the scapula. As a result of these changes, subacromial impingement syndrome, subacromial bursitis, rotator cuff tears, and acromioclavicular joint degeneration may occur. (13).

In order to prevent these problems, it is important to ensure harmony between the shoulder and the scapula muscle activations. EMG biofeedback training can be useful to achieve this harmony. EMG feedback training has been performed in the rehabilitation of patients with nerve injury, torticollis, poliomyelitis, bruxism, and temporomandibular joint syndrome to improve the neuromuscular control of affected muscles and normalization of increased EMG activity (7). Studies have reported that positive changes in muscle activation patterns after the use of EMG biofeedback training (6).

Cleeland (14) reported that the EMG feedback training significantly reduced spasm frequency in patients with spasmodic torticollis. It has been reported that the use of EMG biofeedback training in a patient with a long-term history of the temporomandibular joint syndrome, decreased the tension in the masseter muscle and temporomandibular joint pain (15). Solberg and Rugh (16) reported that ten out of the 15 patients with bruxism showed clinical improvement as a result of EMG feedback training. Ma et al. (17) found that EMG biofeedback training is effective in providing long-term relief from symptoms of impingement. Huang et al. (18) reported that EMG biofeedback training was beneficial in improving the balance ratios of the scapular muscles. In the present study, it was found that EMG biofeedback training, which was included in the traditional rehabilitation program, normalized the increased UT EMG activity. Also, this improvement was preserved at the one-year follow-up. Our results are compatible with the aforementioned studies.

To our knowledge, this study was the first study in the literature in which used EMG biofeedback training in regulating UT muscle activation in the patient with surgically treated fragmented PHF. In this regard, this study can inspire

further studies in which EMG biofeedback training will be used in the regulation of muscle activation in surgically treated fragmented PHF.

Conclusion

The rehabilitation programs, including EMG biofeedback training, can reduce symptoms, improve functional status and quality of life in patients with surgically treated fragmented PHF. However, further long-term randomized controlled studies are needed to examine the effects of EMG biofeedback training on patients with surgically treated fragmented PHF.

Conflict of Interest: None.

Acknowledgment: We would like to thank the case for allowing us to share the details of assessment and treatment in this paper.

Ethical Approval: Informed consent (Verbal and written) was obtained from the case.

Funding: None.

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Physical Inactivity During The COVID-19 Outbreak

COVID-19 Salgını Döneminde Fiziksel Hareketsizlik

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Received: 17/06/2021

Accepted: 15/10/2021

Published Online: 02/11/2021

Abstract

Coronavirus (COVID-19) is one of the pathogens that primarily targets the respiratory. This disease is considered to have emerged in China in late December 2019. The most common initial symptoms of COVID-19's are fever, cough and tiredness. The absence of specific preventive or therapeutic medical interventions for COVID-19 infection and recommendations such as avoiding social interactions and staying at home have emerged to prevent the rate of transmission. To prevent the spread of the COVID-19, governments are taking measures to tighten quarantine and require all citizens to stay at home as much as possible. These measures have harmful consequences for everyone's life. One of them is physical inactivity. It is likely that quarantine at home will cause a decrease in moderate physical activity level and cause sedentary behavior. Fitbit, an American company that develops a wearable device that tracks people's physical activity levels worldwide; reported that the average number of steps in almost all countries decreased from %7 to %38 compared to the same time of last year. This shows that quarantine causes a significant decrease in people's physical activity levels. Given the effects of physical activity on overall and cardiovascular health, it is recommend that people exercise at home. Staying active during quarantine and maintaining a physical exercise routine will be crucial for mental and physical health. During this period, exercise can be done using treadmills, bicycles, fitness balls, elastic bands and weights. Exercises conducted with video and online guided protocols can also be helpful.

Keywords: COVID-19; Quarantine; Physical Inactivity; Physical Activity

Özet

Koronavirüs (COVID-19) öncelikle solunum sistemini hedef alan patojenlerden birisidir. Bu hastalığın Çin'de 2019 yılının Aralık ayının sonlarında ortaya çıktığı değerlendirilmektedir. COVID-19 hastalığının başlangıçtaki en yaygın semptomları ateş, öksürük ve yorgunluktur. COVID-19 enfeksiyonu için spesifik önleyici veya tedavi edici tıbbi müdahalelerin yokluğu ve bulaşma hızını engellemek için bireylerin sosyal etkileşimlerden kaçınması ve evde kalmaları gibi öneriler ortaya çıkmıştır. COVID-19'un yayılmasını engellemek için hükümetler, karantınayı sıkılaştıran ve tüm vatandaşların olabildiğince evde kalmasını gerektiren önlemler almaktadır. Bu önlemlerin herkesin hayatı üzerinde zararlı sonuçları vardır. Bunlardan birisi de fiziksel hareketsizliktir. Evde karantınanın orta şiddetli fiziksel aktivite seviyesinde bir düşüşe neden olacağı ve hareketsiz davranışa neden olması muhtemeldir. Dünya çapında insanların fiziksel aktivite seviyesini takip eden giyilebilir cihaz geliştiren bir Amerikan şirketi olan Fitbit; geçen yılın aynı zamanlarına göre neredeyse tüm ülkelerde ortalama adım sayısının %7'den %38'e kadar azaldığını bildirmişlerdir. Bu da karantınanın insanların fiziksel aktivite seviyelerinde önemli bir düşüşe sebep olduğunu göstermektedir. Fiziksel aktivitenin genel ve kardiyovasküler sağlık durumu üzerindeki etkileri göz önüne alındığında, insanların evde egzersiz yapmaları gerektiği tavsiye edilmektedir. Karantina sırasında aktif kalmak ve fiziksel egzersiz rutinini sürdürmek zihinsel ve fiziksel sağlık için çok önemli olacaktır. Bu dönemde koşu bantları, bisikletler, fitness topları, elastik bantlar ve ağırlıklar kullanılarak egzersizler yapılabilir. Video ve çevrimiçi kılavuzlu protokollerle yürütülen egzersizler de faydalı olabilir.

Anahtar Kelimeler: COVID-19; Karantina; Fiziksel Hareketsizlik; Fiziksel Aktivite

Cite this article: Canlı M, Kaya MH., Buyukturan O., Buyukturan B., Kara E. Physical Inactivity During The COVID-19 Outbreak. Turk J Health S. 2021;2(3):pp.59-63.



GİRİŞ

Koronavirüs hastalığı 2019 (COVID-19), yeni keşfedilen bir koronavirüsün neden olduğu bulaşıcı hastalıktır. Önceki koronavirüs salgınları daha önce büyük bir halk sağlığı tehdidi olan ajanlar olarak karakterize edilen şiddetli akut solunum sendromu (SARS) ve Ortadoğu solunum sendromunu (MERS) içerir. 2019 yılının Aralık ayının sonlarında bir grup hasta bilinmeyen bir etiyolojiyle ilk pnömoni tanısıyla hastanelere başvurmuştur. Bu hastalığın Çin'in Hubei eyaletine bağlı Wuhan şehrinde deniz ürünleri ve toplu hayvan satış pazarında ortaya çıktığı değerlendirilmektedir.(1, 2)

COVID-19'a yakalanan kişilerin semptomları ilk olarak yaklaşık ortalama 5.2 gün sonra inkübasyon döneminin ardından ortaya çıkar.(3) COVID-19 semptomlarının başlangıcından virüsün ölümüne kadar geçen süre ortalama 14 gün olmakla birlikte 6 ila 41 gün arasında değişmektedir. Bu süre hastanın yaşına ve bağışıklık sisteminin durumuna göre değişmektedir.(4) COVID-19 hastalığının başlangıçtaki en yaygın semptomları ateş, öksürük ve yorgunluktur diğer semptomlar ise balgam üretimi, ishal ve nefes darlığıdır.(4-6)

COVID-19 enfeksiyonu için spesifik önleyici veya tedavi edici tıbbi müdahalelerin yokluğu, hızlı bulaşma hızı ve görünüşte önemli ölçüde belgelenmemiş kontaminasyon ve bulaşma sayılarının yanı sıra, bireylerin sosyal etkileşimlerden kaçınmak, hastalığın yayılmasını engellemek için evde kalmaları gerektiği konusunda bilimsel olarak sağlam bir öneriye yol açmıştır ve böylece dünya çapında sağlık sistemleri üzerindeki yük azaltılmaya çalışılmıştır. Ancak enfeksiyonun kontrol altına alınması için böyle bir müdahalenin yapılmasının potansiyel davranışsal ve klinik sonuçları bulunmaktadır(7).

COVID-19'un yayılmasını engellemek için hükümetler, karantınayı sıkılaştıran ve tüm vatandaşların olabildiğince evde kalmasını gerektiren önlemler alınmıştır. Bu önlemlerin herkesin hayatı üzerinde zararlı sonuçları vardır. Bunun yanı sıra, fiziksel hareketsizliğinde zararlı etkileriyle ilgili ciddi bir endişe vardır. Bu dönemde tüm spor aktiviteleri askıya alınmış veya iptal edilmiştir. İnsan damlacıkları, fiziksel aktiviteler sırasında ve özellikle grup aktivitelerinde ana aracı olduğundan, hiperventilasyon, önerilen sosyal mesafenin 1.5 m olarak korunmasına rağmen enfeksiyon riskini artırır. Çevresel ve hasta koşullarının çeşitli kombinasyonları altında, her boyuttaki damlacıkların 7-8 m'ye kadar gidebildiği bildirilmiştir.(8) Bununla birlikte, bildiğimiz kadarıyla, koşma veya bisiklete binme gibi zorlu egzersiz aktiviteleri sırasında damlacık yayılmasını araştıran titiz bir çalışma yoktur. Dolayısıyla bir yandan fiziksel aktivitenin sınırlandırılması COVID-19 salgınına önlemeye hizmet ederken, diğer yandan bu kesinlikle fiziksel aktivitelerin ani kesintiye uğraması ve/veya ciddi şekilde sınırlandırılmasıyla ilgili birçok problemi beraberinde getireceği belirtilmiştir.(9)

Evde karantınanın orta-şiddetli (150 dk/hafta) fiziksel aktivite seviyesinde bir düşüşe neden olduğu ve hareketsiz davranışa neden olması muhtemeldir.(10) Dünya çapında fiziksel aktivite seviyeleri üzerindeki gerçek etkisi gösterilmeyi sürdürse de, bir bireyin fiziksel aktivite seviyesini takip eden giyilebilir cihazlar geliştiren bir Amerikan şirketi olan Fitbit son zamanlarda 30 milyon kullanıcının fiziksel aktivite seviyesini paylaştı. Sonuçlara göre geçen yılın aynı zamanlarına göre neredeyse tüm ülkelerde ortalama adım sayısında bir azalma vardı (%7'den %38'e kadar). Bu ön kanıt karantınanın insanların fiziksel aktivite seviyelerinde önemli bir düşüşe sebep olduğunu göstermektedir.(11, 12) Aslında koronavirüs salgınının öncesinde de fiziksel hareketsizlik salgını ile karşı karşıya kalınmıştır. Mevcut veriler dünya nüfusunun %31'inin fiziksel aktivite için minimum önerileri karşılamadığını ve 2009'da küresel hareketsizlik prevalansının %17 olduğunu belirtmektedir.(13) Bazı ülkelerde boş zaman (isteğe bağlı) fiziksel aktivitede umut verici olumlu eğilimlere rağmen fiziksel aktivite düzeyleri halen yeterli düzeyde değildir. (14-17) Fiziksel hareketsizliğin küresel olarak yaygınlaşması taşıdığı risklerle daha da artmaktadır. Lee ve ark.(18) dünya çapında bulaşıcı olmayan hastalıklardan kaynaklanan tüm ölümlerin %6-10'unun fiziksel hareketsizliğe atfedileceği ve bu oranın bazı hastalıklar içinde ölüm yüzdelerinden daha yüksek olduğunu belirtmişlerdir.(19) Örneğin 2007 yılında yapılan bir çalışmada eğer fiziksel olarak aktif olmayan insanlar yeterince aktif olsaydı 5.3-5.7 milyon ölümün teorik olarak önlenebilir olacağı belirtilmiştir.(20)

Dünya genelinde yetişkinler arasında yüksek bir fiziksel hareketsizlik yaygınlığı vardır.(21, 22) Bu büyük bir endişe kaynağıdır çünkü fiziksel hareketsizlik, kronik hastalıklar ve erken ölümle ilişkili bir risk faktörüdür.(23-25) Buna paralel olarak, kronik hastalıkların hem gelişmiş hem de gelişmekte olan ülkelerde sağlık hizmetleri maliyeti üzerinde önemli bir yüke sahip olduğunu tespit eden çalışmalar yapılmıştır.(26-28) Kronik hastalıklar, özellikle diyabetle ilgili daha yüksek harcamalar ve sağlık hizmetleri ile ilişkilendirilmiştir. Meksika sağlık sisteminde kronik hastalıklarla ilişkili sağlık bakım maliyetlerindeki artış, 2 yıllık bir dönemde beklenenden daha yüksek olmuştur.(26) Brezilya'da yakın zamanda yapılan bir çalışmada(26), aşırı kilo ve obezite ile ilgili tüm hastalıkların toplam yıllık maliyeti yaklaşık 2.1 milyar ABD doları olarak hesaplanmıştır; bu, tüm ayakta tedavi maliyetlerinin yaklaşık %10'unu temsil etmektedir. Amerika Birleşik Devletleri'nde Hogan ve ark.(28) diyabet kontrol harcamaları için ilaçlarla ilgili doğrudan ve dolaylı maliyetlerin 132 milyar ABD doları olduğunu bulmuştur. Halk sağlığı harcamalarına yönelik artan taleple mücadele etmek için stratejiler formüle edilmiş ve karşılığında, fiziksel aktivitenin teşvik edilmesi sağlık harcamalarının azaltılmasında ilgili yatırım olarak belirtilmiştir.(29) Bunun temel nedeni, kronik hastalıkları olan kişilerde bile daha yüksek alışılmış fiziksel aktivitenin

daha düşük ilaç kullanımı ve sağlık hizmetleri maliyetleri ile bağlantılı olmasıdır.(30, 31) Bu veriler ışığında koronavirus salgınından kurtulsak bile fiziksel aktivite yetersizliğinin yıllarca devam edeceği görülmektedir.

COVID-19 Döneminde Fiziksel Aktivitenin Önemi ve Öneriler

Dünya Sağlık Örgütü (WHO) tarafından yayınlanan Fiziksel Aktivite Küresel Eylem Planı” bulaşıcı olmayan hastalıkların önlenmesi için fiziksel aktivitenin zorunlu olduğunu belirtmiştir(32). Bunun nedeni düzenli fiziksel aktivitenin, kardiyovasküler hastalıklara yakalanma risklerini azaltması ile ilişkilidir.(32-34) “2019 Kardiyovasküler Hastalığın Birincil Önlenmesine İlişkin Kılavuz” da yetişkinler için haftada en az 150 dakika orta yoğunlukta veya haftada 75 dakika şiddetli aerobik egzersiz yapılmasının kardiyovasküler hastalık riskini azalttığı belirtilmiştir.(35) Arnett ve ark. yapmış oldukları bir çalışmada uzun süre TV izlemenin Tip 2 Diyabet Mellitus, kardiyovasküler hastalıklara neden olduğunu ve bu nedenlere bağlı ölümlerle ilişkilendirmişlerdir.(34) Hareketsiz kalma süresinin uzaması, fiziksel aktivite düzeylerinden bağımsız olarak zararlı sağlık sonuçlarıyla ilişkili olduğu belirtilmiştir. Karantina sırasında hükümetler, açık havada egzersiz ve sosyal aktivitelerin büyük çoğunluğunu yasaklayarak fiziksel aktivitenin azalmasına neden olmuşlardır. İnflamasyon; obezite, Tip 2 Diyabet ve kardiyovasküler hastalıklar gibi kronik hastalıkların altında yatan patofizyolojik bir süreçtir. Düzenli fiziksel aktivite inflamasyonu ve oksidatif stresi azaltır ve normal kilonun korunmasına, visseral yağ birikiminin azaltılmasına yardımcı olduğu bilinmektedir.(32, 33) COVID-19 salgını döneminde toplu karantinanın bir sonucu olarak sınırlı fiziksel aktivite ve kişinin evinden düzenli bir yürüyüşe çıkmaması, kardiyovasküler riski artıracak birkaç metabolik etkiyle ilişkilendirilmiştir. Ayrıca, fiziksel egzersize yanıt olarak bir çok yararlı metabolik ve kardiyovasküler ayarlanmanın, sadece iki haftalık hareketsizlik sonucu aerobik kapasiteyi bozduğunu ve/veya kan basıncının artmasına sebep olduğu bildirilmiştir. Egzersizin aniden kesilmesi, kas dokusunda insülin direncine ve kas glukoz kullanımının azalmasına sebep olduğu bildirilmiştir.(36)

Fiziksel aktivitenin genel ve kardiyovasküler sağlık durumu üzerindeki olumlu etkileri göz önüne alındığında, insanların evde egzersiz yapmaya devam etmesi tavsiye edilir. Koşu bantları, bisikletler, fitness topları, elastik bantlar ve ağırlıkların kullanılması tavsiye edilir. Video ve çevrim içi kılavuzlu protokollerle yürütülen egzersizler çok faydalı olabilir. Yerel makamlar mümkün olduğunca, kişiler arası yeterli mesafe (1.5 m’den fazla) olan açık hava egzersiz etkinliklerine izin vermelidir(9). Bu kapsamda damlacıkların ulaştığı mesafenin de araştırılması gerekmektedir.

Karantina sırasında aktif kalmak ve fiziksel egzersiz rutinini sürdürmek zihinsel ve fiziksel sağlık için çok önemli

olacaktır.(37-39) Dünya Sağlık Örgütü, akut solunum yolu hastalığının herhangi bir semptomu veya teşhisi olmayan, kendi kendine karantina altındaki kişilere yönelik, evde nasıl aktif kalınacağına ve hareketsiz davranışın nasıl azaltılacağına dair pratik tavsiyeler içeren bir kılavuz yayınladı. Çevrimiçi egzersiz derslerini takip etmeyi ve evde video veya uygulama rehberliğinde aerobik eğitimi kullanmayı öneriyorlar. Tablo 1.(40) Dünya Sağlık Örgütünün; “Kendi kendine karantina sırasında fiziksel olarak aktif kalın” sözünü özetlemektedir.

SONUÇ

Sonuç olarak COVID-19 salgınının, insanları hem fizyolojik hem de psikolojik olarak etkilediği görülmektedir. Bu karantina sürecinde evde aktif kalınmalı ve düzenli egzersiz yapılmalıdır. İnsanlar her halükarda mümkün olduğunca evde egzersiz yapmaya teşvik edilmelidir. Tek başına spor yapmak veya egzersiz yaparken maske takmak doğru bir adım olabilir. Egzersiz önerileri almak ve egzersizlerin doğru yapıldığını onaylatmak için fizyoterapistlerle iletişime geçilmesi gerekebilir ve telerehabilitasyon hizmetleri kullanılabilir. Salgının süresinin belirsizliği nedeniyle insanların kronik hastalıklara yakalanma riskini azaltabilmek amacıyla egzersize yönlendirilmesinin gerektiğini düşünmekteyiz.

Tablo 1. Dünya Sağlık Örgütü COVID-19 salgın döneminde fiziksel aktivite kılavuzu

Gün içerisinde kısa aktif molalar verin. Kısa fiziksel aktivite süreleri haftalık önerilere eklenir. Aşağıda önerilen aktiviteleri her gün aktif olmak için ilham kaynağı olarak kullanabilirsiniz.
Dans etmek, çocuklarla oynamak, temizlik, bahçe işleri gibi aktiviteleri yapmak, evde aktif kalmanın yollarıdır.
Online bir egzersiz dersini takip edin. Online egzersiz sınıflarının zenginliğinden yararlanın. Bunların çoğu ücretsizdir ve Youtube’da bulunabilir. Tecrübeniz yoksa dikkat edin.
Yürü. Küçük alanlarda dolaşmak veya yerinde saymak yürümek aktif kalmanıza yardımcı olabilir. Telefonla konuşuyorsanız oturmak yerine ayakta durun veya evin içerisinde yürüyün. Yürümek veya egzersiz yapmak için dışarı çıkabiliyorsanız diğer insanlardan en az 1 metre uzakta olduğunuzdan emin olun.
Ayağa kalk. Mümkün olduğunca ayağa kalkarak hareketsiz kalma sürenizi azaltın. İdeal olarak 30 dakikada bir oturma ve uzanma sürelerini kısaltmayı amaçlayın. Ayakta çalışmaya devam etmek için yüksek bir masa kullanarak veya bir yığın kitap veya diğer malzemeleri üst üste koyarak ayakta bir masa kurmayı düşünün.
Rahatlayın. Meditasyon ve derin nefes alıp vermek sizin kalmanıza yardımcı olabilir.
Sağlıklı beslenin ve susuz kalmayın. Dünya Sağlık Örgütü şekerli içecekler yerine su içmesini önermektedir. Yetişkinler için alkolü içecekleri sınırlayın veya bunlardan kaçının, gençlerde bunlardan kesinlikle kaçının. Bol meyve ve sebze bulundurun, tuz, şeker ve yağ alımını sınırlayın.

Finansal Kaynak: Bu çalışma sırasında, yapılan araştırma konusu ile ilgili doğrudan bağlantısı bulunan herhangi bir ilaç firmasından, tıbbi alet, gereç ve malzeme sağlayan ve/veya üreten bir firma veya herhangi bir ticari firmadan, çalışmanın değerlendirme sürecinde, çalışma ile ilgili verilecek kararı olumsuz etkileyebilecek maddi ve/veya manevi herhangi bir

destek alınmamıştır.

Çıkar Çatışması: Bu çalışma ile ilgili olarak yazarların ve/veya aile bireylerinin çıkar çatışması potansiyeli olabilecek bilimsel ve tıbbi komite üyeliği veya üyeleri ile ilişkisi, danışmanlık, bilirkişilik, herhangi bir firmada çalışma durumu, hissedarlık ve benzer durumları yoktur.

Yazar Katkıları: Fikir/Kavram: Öznur Büyükturan, Buket Büyükturan; Tasarım: Mehmet Canlı, Mehmet Hanifi KAYA; Denetleme/Danışmanlık: Öznur Büyükturan, Buket Büyükturan; Veri Toplama ve/veya İşleme: Mehmet Canlı, Mehmet Hanifi KAYA; Analiz ve/veya Yorum: Öznur Büyükturan, Buket Büyükturan, Mehmet Canlı, Mehmet Hanifi KAYA; Kaynak Taraması: Mehmet Canlı, Mehmet Hanifi KAYA, Ersan KARA; Makalenin Yazımı: Öznur Büyükturan, Buket Büyükturan, Ersan KARA; Eleştirel İnceleme: Öznur Büyükturan.

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