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Research Article / Araştırma Makalesi

Effect of androgen deprivation therapy on plasma irisin levels, muscle strength, and physical functions tests of lower extremities

Androjen deprivasyon tedavisinin plazma irisin düzeyine, kas kuvvetine ve alt ekstremitenin fiziksel fonksiyon testlerine etkisi

Ayhan Canbulut[1], Sabriye Ercan[1], Sefa Alperen Öztürk[2], Alper Özorak[2], Fevziye Burcu Şirin[3], Hülya Mete Arıcan[3], Cem Çetin[1]

[1]*Sports Medicine Department, Faculty of Medicine, Süleyman Demirel University, Isparta, Türkiye*
[2]*Urology Department, Faculty of Medicine, Süleyman Demirel University, Isparta, Türkiye*
[3]*Medical Biochemistry Department, Faculty of Medicine, Süleyman Demirel University, Isparta, Türkiye*

ABSTRACT

Objective: Losses in muscle strength and decreases in physical functions, and therefore a decrease in quality of life, have been observed in prostate cancer patients receiving androgen deprivation therapy (ADT). Irisin is a new exercise-induced myokine, released from the muscles. It is predicted that muscle tissue irisin release as a result of muscle loss, may be affected in patients receiving ADT. The aim of this study is to compare irisin levels, together with muscle strength and physical functions, in patients receiving ADT, patients not receiving ADT, and healthy individuals.

Material and methods: A total of 21 healthy individuals (control group: CG); 28 local- or local-advanced prostate cancer patients, not receiving ADT (non-ADT group); and seven prostate cancer patients receiving luteinizing hormone releasing hormone agonist (ADT group) were included in the study. Blood biochemistry (lipid profile, hormones, prostate specific antigen, glucose, insulin, and creatine phosphokinase) and irisin analyses were conducted. Physical functions were assessed by using the Five Times Sit to Stand (5TSTS), climbing stairs, walking pace, and functional reach (FRT) tests. Lower extremity isometric muscle strength was measured using an isokinetic dynamometer.

Results: It was observed that the 5TSTS test results were higher (p=0.03), but FRT results were lower (p=0.04) in the ADT group. It was found that isometric muscle strength in lower extremities was significantly lower in the ADT group (p<0.05). Plasma irisin levels did not reveal a significant difference between the groups (p=0.31).

Conclusion: It was determined that muscle strength and physical function test performances of prostate cancer patients receiving ADT were worse, but their irisin levels were similar to patients who were not receiving ADT, and the healthy CG. Muscle strength and physical functions of patients who are receiving ADT, and who will start receiving ADT should be monitored, and protective measures should be taken.

Keywords: *Irisin, prostate cancer, isometric muscle strength, androgen deprivation therapy, physical function*

ÖZ

Amaç: Androjen deprivasyon tedavisi (ADT) alan prostat kanseri hastalarında kas kuvveti kaybı ve fiziksel fonksiyonlarda düşüşler gözlenmekte, bunun sonucunda yaşam kalitelerinin de düşmektedir. İrisin; egzersiz sonrasında kastan salınan bir miyokindir. ADT alan hastalarda, özellikle kas dokusu kaybı sonucu salınan irisin düzeyinin etkilenebileceği öngörülmektedir. Çalışmamızın amacı ADT alan, ADT almayan prostat kanseri hastalarının ve sağlıklı bireylerin kas kuvveti ve fiziksel fonksiyonlarıyla irisin düzeylerini karşılaştırmaktır.

Gereç ve Yöntem: Çalışmaya; herhangi bir kanser tanısı konulmamış 21 sağlıklı birey (kontrol grubu: KG), lokal ve lokal ileri prostat kanseri olup ADT almayan 28 hasta (non-ADT grubu) ve ADT olarak LHRH agonisti alan yedi prostat kanseri hastası (ADT grubu) katıldı. Kan örneklerinde biyokimyasal (lipid profili, hormonlar, prostat spesifik antijen, glükoz, insülin ve kreatin fosfokinaz testleri) ve irisin analizleri yapıldı. Katılımcıların fiziksel fonksiyonları beş kez otur kalk, merdiven çıkma, yürüme hızı ve fonksiyonel uzanma testi (FUT) ile değerlendirildi. İzokinetik dinamometre ile alt ekstremite izometrik kas kuvveti ölçüldü.

Bulgular: ADT grubunun; beş kez otur kalk test sonucunun daha yüksek (p=0.03) ve FUT sonucunun daha düşük (p=0.04) olduğu gözlendi. Alt ekstremite izometrik kas kuvvetinin ADT grubunda anlamlı derecede düşük olduğu belirlendi (p<0.05). Plazma irisin düzeylerinde ise gruplar arasında anlamlı farklılık gözlenmedi (p=0.31).

Sonuç: ADT alan prostat kanseri hastalarının kas kuvvetinin ve fiziksel fonksiyon test (beş kez otur kalk, FUT) performanslarının düşük olduğu gözlendi; fakat irisin düzeyleri ADT almayan hastalar ve sağlıklı kontrol grubu ile benzer bulundu. ADT alan ve ADT almaya başlayacak hastaların kas kuvveti ve fiziksel fonksiyonları izlenmeli ve koruyucu önlemler alınmalıdır.

Anahtar Sözcükler: *İrisin, prostat kanseri, izometrik kas kuvveti, androjen deprivasyon tedavisi, fiziksel fonksiyon*

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Correspondence / Yazışma: Sabriye Ercan · Süleyman Demirel Üniversitesi, Tıp Fakültesi, Spor Hekimliği Bölümü, Isparta, Türkiye · sabriyeercan@gmail.com

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INTRODUCTION

According to GLOBOCAN data, prostate cancer was the second prevalent cancer type in men, in 2020 (1). Androgens are required for prostate function in healthy men. However, prostate cancer cells exhibit an over-activation of the androgen signal path and cause uncontrolled proliferation of tumour cells. Therefore, androgen deprivation therapy (ADT) is frequently used in prostate cancer treatment to reduce androgen levels in the circulation (2).

Almost half of prostate cancer patients receive ADT at some stage of their treatment (3). Bilateral orchiectomy has given way to pharmacological agents today due to negative effects (2). Pharmacological agents, such as luteinizing hormone releasing hormone (LHRH) agonists and antagonists, steroidal anti-androgens, and non-steroidal anti-androgens are used alone or in combination in ADT (4).

While ADT increases life expectancy, it causes adverse effects, such as metabolic diseases, sexual dysfunction, gynecomastia, depression, hot flashes, anaemia, decrease in bone mineral density, neuro-cognitive changes and changes in body composition (5,6). Increase in body weight, body fat ratio, insulin resistance, fasting glucose levels, and metabolic diseases can also be seen in patients receiving ADT. These metabolic changes negatively affect the quality of life (QoL) of patients (6).

Another significant adverse effect of ADT is decrease in physical performance followed by a decrease in muscle mass and strength (3). As a result, increased fragility and decreased independency and QoL are observed in patients (7). Although the mechanism of the effects of ADT on skeletal muscle is not understood exactly, it is thought that it could be multifactorial. Decreased muscle mass, and muscle fat infiltration (myosteatosis) can cause a decrease in muscle strength. This can lead to loss of balance (7,8).

It is known that a physically active lifestyle is protective against chronic diseases (9). It is thought that the positive effects of exercise on the metabolism and skeletal muscle are realised through myokines such as irisin that are released during exercise. Irisin is a newly found myokine increased in the circulation following exercise (10). Irisin also increases mitochondrial UCP1 expression via an unidentified receptor in fat tissue (11), and thermogenesis and energy generation by functioning a protein resolver in UCP1 mitochondrial membrane (12). Thus, it speeds up the metabolisms of glucose and lipids related to energy consumption (13). Irisin is hypothesized to have direct effects on many malignancies in addition to all these other effects (10). There is high correlation between increased physical activity after diagnosis and reduced prostate cancer progression and mortality, and it has been discovered that exercise-induced myokines such irisin may play a role in suppressing prostate cancer (14).

ADT can affect metabolic status, body composition, and susceptibility to sarcopenia as a result of changes in muscle (6). The fact that physical functions may be affected together with an effect on muscle tissue may aggravate the extent of cancer-related fatigue in prostate cancer patients. With the combined effect of all these factors, quality of life may change. The effects of ADT on muscle tissue may affect the level of irisin released from muscle. The aim of this study was to compare the metabolic status, fatigue, activity participation level, quality of life, lower extremity function, muscle strength, and irisin levels of prostate cancer patients receiving and not receiving ADT, with those of healthy individuals.

MATERIAL and METHODS

Participants: Included in the study were 56 voluntary individuals who had applied to the urology clinic at our hospital between August 2020 and January 2021. While 28 participants, who had been diagnosed with a local- or locally-advanced prostate cancer, and who had not received ADT previously were placed in the non-ADT group; seven participants receiving LHRH agonist were placed in the ADT group. Additionally, 21 participants of similar age, without any malignancy diagnosis formed the control group (CG).

For the prostate cancer patients, exclusion criteria were determined as being younger than 50 years of age, receiving or having received chemotherapy/radiotherapy, having metastasis, having a neuromuscular disease, and having communication problems. For all the groups, having done aerobic or resistance exercises in the last 12 months was also an exclusion criterion. Other chronic diseases in the patient group, such as diabetes mellitus, obesity, metabolic syndrome etc. were inquired during anamnesis. If exclusion criterions were present, those patients were excluded.

The study was approved under decision number 38, dated 13.02.2020, by the Local Ethical Committee. Permissions were obtained from the Ministry of Health, Pharmaceuticals and Medical Devices Agency for the observational drug study.Informed consents were obtained from the participants.

Collecting blood samples, and biochemical analyses: Venous blood samples were taken after 12-h of fasting, between 08:30 and 10:30 AM, into gel-barrier blood collecting tubes and EDTA containing tubes. The samples were centrifuged at 3000 rpm for 10 min. Serum samples were analysed for the insulin test with electroluminescence immunoassay method (Cobas 6000, Roche Diagnostics, Germany); thyro–

id-stimulating hormone (TSH), total prostate-specific antigen (PSA), total testosterone, oestradiol tests were conducted with chemiluminescence immunoassay method (Beckman Coulter DXI 800, Beckman Coulter, USA); glucose, creatine phosphokinase (CPK), cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C) tests were conducted with spectrophotometric method (Beckman Coulter AU 5800, Beckman Coulter, USA) in line with manufacturers' direction. Low-density lipoprotein-cholesterol (LDL-C) levels were calculated with the Friedewald formula.

Remaining samples were separated into Eppendorf tubes, and stored at -80 °C until testing for free testosterone and irisin levels. The quantitative measurement of the serum free testosterone levels and plasma irisin levels were conducted using competitive ELISA methods, following the procedures of the commercial kit (Free Testosterone ELISA, DRG Instruments GmBH, Germany; Catalogue no: EIA-2924; Irisin, Recombinant ELISA, Phoenix Pharmaceuticals, USA; Catalogue no: EK-067-29).

Body composition analysis: Height measurement (SECA 700, Germany) and body composition analyses (Tanita Body Fat Analyzer, Model BC 418) of the participants were performed after a 12-h fasting.

Physical function tests: Lower extremity functions of the participants were evaluated using: 1) the Five Times Sit to Stand test (5TSTS), 2) the stair climbing test, 3) the functional reach test (FRT), and 4) the 4-m walking pace test.

1) In the 5TSTS test, the durations were measured in seconds for participants reaching the stand-up position from a sitting position for five times. The prolongation of duration reflects negativity in physical function (3,15).

2) In the stair climbing test, the durations were measured in seconds for participants climbing up and down nine steps of stairs. The prolongation of duration reflects negativity in physical function (3,15).

3) The reach distance in the FRT was measured in cm. The increase in distance reached reflects positiveness in physical function (16).

4) The 4-m walking pace was calculated in m/s. The prolongation of duration reflects negativity in physical function (17).

Lower extremity muscle strength measurement: Isometric muscle strengths of participants with the knee at 60° flexionwere measured with an isokinetic dynamometer (Isoforce, Tur Kinetics, Germany). The test was conducted with five (three hamstring, two quadriceps) repetitions (18). Mean scores for the left and right extremities were used in the analyses.

Other measurements

SARC-F scale: The strength, assistance walking, rise from a chair, climb stairs, and falls (SARC-F) scale (19,20) was used to screen sarcopenia risk. A total score of ≥4 is considered to be risky for sarcopenia (21).

The International Physical Activity Questionnaire (IPAQ)-Short Form: The IPAQ-Short Form was used to determine activity levels in the previous week (22,23).

The 36-Item Short-Form Survey (SF-36): The SF-36 survey that consists of eight sub-factors (24) was used to determine QoL. Low scores indicate negativity in health (25).

The Fatigue Severity Scale (FSS): The FSS scale was used to determine fatigue severity (26). Scores ≥4 indicate severe fatigue (27).

Power Analysis and Statistical Method

Sample size for groups was calculated (G*Power v3.1 software) as n=7, with an α error level of 0.05, power of 0.80, and impact force of 1.74. Statistical analyses of the study were conducted using SPSS v.23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as means ± standard deviation and frequency (n, %). Normality of the data was analysed using Shapiro-Wilk test. Kruskal-Wallis or one-way ANOVA method were used in comparisons with multiple independent groups. Monte Carlo corrected chi-square analysis was used in determining the correlations between categorical variables. A $p<0.05$ was accepted as statistically significant.

RESULTS

Descriptive data: Data from 56 participants were analysed. No significant differences were found between the descriptive data ($p>0.05$, Table 1). In the ADT group, treatment continued for 8.4±9.7 months.

Table 1. Descriptive data

Parameter	CG (n=21)	non-ADT (n=28)	ADT (n=7)	p
Age (yrs)	64.1±5.5	64.8±5.8	69.4±4.2	0.09
Body mass index (kg/m²)	27.9±4.4	30.2±3.6	30.5±5.0	0.13
Fat free mass(kg)	58.5±7.8	61.9±5.8	59.1±5.7	0.20
Fat ratio (%)	26.0±6.8	28.3±5.6	31.1±4.7	0.13
Fat mass (kg)	21.5±8.9	24.8±7.2	27.5±8.5	0.18

CG: control group, ADT: prostate cancer patients receiving LHRH agonist, non-ADT: patients not receiving ADT

Biochemistry and irisin analyses: Oestradiol, total- and free-testosterone levels of individuals in the ADT group were low (Table 2). This result indicates that ADT is applied by the patients. No differences were found in the biochemical markers indicating the cardiometabolic status, or the plasma irisin levels (p>0.05).

Table 2. Blood chemistry

Parameter	CG (n=21)	non-ADT (n=28)	ADT (n=7)	p
Total cholesterol(mg/dl)	213.9±48.9	220.0±54.4	205.8±33.7	0.91
Triglyceride(mg/dl)	142.9±78.2	223.1±135.4	159.7±103.0	0.05
LDL-cholesterol(mg/dl)	133.9±40.3	128.7±37.5	120.3±32.4	0.71
HDL-cholesterol(mg/dl)	51.4±11.9	48.4±9.8	53.6±14.0	0.44
Oestradiol(pg/ml)	21.8±5.9^{a}	25.2±5.8^{b}	11.0±8.6^{a,b}	**0.0001***
Total testosterone(ng/dl)	319.2±100.4^{a}	360.6±84.3^{b}	75.6±112.3^{a,b}	**0.0001***
Free testosterone(pg/ml)	10.1±3.9	11.5±2.4^{a}	4.5±5.1^{a}	**0.006***
TSH(µIU/ml)	1.7±1.0	1.6±1.4	1.3±0.3	0.76
PSA (ng/dl)	2.1±3.0	3.7±6.6	1.2±2.0	0.09
Glucose(mg/dl)	112.3±24.1	118.9±31.0	114.7±17.9	0.61
Insulin(µIU/ml)	15.1±18.3	15.7±13.7	21.6±25.9	0.71
CPK (U/L)	107.8±65.3	135.5±129.8	98.5±35.8	0.95
Irisin(ng/ml)	17.0±1.0	17.2±1.1	16.4±1.3	0.31

*: p significant at 0.05 level; ^{a,b}: between groups post-hoc test significant at 0.05 level. CG: control group; ADT: patients receiving LHRH agonist; non-ADT: patients not receiving ADT. PSA: prostate specific antigen; TSH: thyroid stimulating hormone; CPK: creatine phosphokinase

Questionnaire and scales: No significant differences were found between the groups for the measurement tool results (p>0.05, Table 3).

Table 3. SARC-F, FSS, IPAQ and SF-36 scores

Parameter	CG (n=21)	non-ADT (n=28)	ADT (n=7)	p
SARC-F (score)	0.05±0.20	0.1±0.4	0.4±1.1	0.65
FSS (score)	2.3±1.6	2.6±1.9	3.5±2.0	0.49
IPAQ (MET-min/week)	858.5±628.3	678.2±633.3	459.6±445.1	0.12
SF-36 (score)				
Physical function	91.4±8.8	87.1±11.9	78.6±16.0	0.16
Role physical	79.8±35.9	73.2±40.2	57.1±53.4	0.56
Role emotional	88.9±30.4	75.0±35.8	76.2±41.8	0.22
Vitality	59.0±19.5	61.6±18.1	55.7±16.4	0.66
Mental health	55.8±14.4	62.3±14.8	60.0±18.5	0.18
Social functioning	76.2±15.3	73.7±15.7	78.6±13.9	0.53
Bodily pain	67.1±22.0	70.6±23.4	72.1±20.1	0.78
General health	50.5±14.7	55.4±13.2	51.4±8.5	0.27

CG: control group; ADT: prostate cancer patients receiving LHRH agonist; non-ADT: patients not receiving ADT; IPAQ: International Physical Activity Questionnaire; FSS: Fatigue Severity Scale; SF-36: 36-Item Short-Form Survey; SARC-F: Strength, Assistance Walking, Rise from a Chair, Climb Stairs, and Falls

Lower extremity functions: The walking pace and stair climbing test durations of the groups were similar (p>0.05). On the other hand, the 5TSTS test results were higher (p=0.03) and FRT results were lower (p=0.04) in the ADT group (Table 4).

Table 4. Comparison of physical function test results among the groups

Test	CG (n=21)	non-ADT (n=28)	ADT (n=7)	p
Walking pace (m/s)	1.1±0.2	1.1±0.1	1.1±0.2	0.36
5TSTS (s)	11.0±1.7[a]	11.2±2.1[b]	13.3±2.1[a,b]	**0.03***
FRT (cm)	39.4±3.6[a]	39.9±5.4[b]	36.0±2.4[a,b]	**0.04***
Stair climbing test(s)	10.9±1.5	11.2±1.5	12.3±1.8	0.16

*: p significant at 0.05 level; [a,b]: between-groups post-hoc test significant at 0.05 level; CG: control group; ADT: patients receiving LHRH agonist; non-ADT: patients not receiving ADT; FRT: functional reach test, 5TSTS: five times sit to stand

Lower extremity muscle strength: It was found that quadriceps and hamstring isometric strength of participants in the ADT group was significantly lower (p<0.05, Table 5).

Table 5. Lower extremity muscle strength measures

	CG (n=21)	non-ADT (n=28)	ADT(n=7)	p
Q MMT (Nm)	149.6±33.3[a]	140.1±31.8[b]	102.8±21.4[a,b]	**0.008***
Q peak torque (Nm)	185.1±36.6[a]	171.4±37.7[b]	129.8±28.9[a,b]	**0.004***
Q peak torque/BW(Nm/kg)	2.4±0.7[a]	2.0±0.5[b]	1.5±0.3[a,b]	**0.003***
H MMT (Nm)	38.1±7.1[a]	40.1±7.0[b]	32.3±6.2[a,b]	**0.03***
H peak torque (Nm)	47.5±8.2	47.9±9.1	40.2±7.4	0.07
H peak torque/BW(Nm/kg)	0.61±0.10[a]	0.56±0.10	0.50±0.10[a]	**0.04***

*: p significant at 0.05 level; [a,b]: between-groups post-hoc test significant at 0.05 level; CG: control group, ADT: patients receiving LHRH agonist; non-ADT: patients not receiving ADT; MMT: maximum mean torque, Q: quadriceps, H: hamstring, BW: body weight

DISCUSSION

At the end of the study, three important results emerge: 1) Patients receiving ADT performed worse in some functional tests, 2) The isometric muscle strength was lower in patients receiving ADT, 3) Plasma irisin levels did not display any differences between the groups.

Cardiometabolic parameters and irisin levels did not yield any significant difference between the groups. The occurrence of cardiometabolic effects is affected by a variety of variables. The short duration of ADT therapy may be a reason for lack of difference reported in the study. In contrary, there are gaps in the literature on the physiopathological mechanism of action of irisin, which may have made it difficult to support the hypothesis of the study.

Muscle strength of patients receiving ADT was evaluated with the one-maximum repetition (1 RM_{max}) method, isotonic muscle strength was used in the literature (3). In this study, the isometric muscle strength of patients was evaluated using an isokinetic dynamometer, and differences between groups were found. In studies applying direct assessment methods and special equipment, such as an isokinetic dynamometer, for measuring muscle strength, differences in strength are conceivable.

Galvao et al. (28), found that patients receiving ADT had lower 6-m walking pace, 6-m reverse tandem walking pace, 400-m walking test, and 5TSTS test scores. In the current study, it was similarly found that patients receiving ADT had lower 5TSTS test cores (p=0.03); while walking pace was similar for all groups. Galvao et al. measured balance with the 6-m reverse tandem walking test and observed that patients receiving ADT had lower performance. Balance assessed by FRT was also low in patients receiving ADT. In the same study, isotonic muscle strength (for rowing, bench press, leg extension) was found lower in patients receiving ADT, with no differences in the leg press test results (28). In the current study, it was observed that lower extremity isometric muscle strength was lower in patients receiving ADT.

Similarly, Newton et al. (3) showed that patients starting ADT had lower walking pace and stair climbing scores within six months. While participants' rowing and bench press isotonic muscle strength decreased, there was no difference in the leg press results. In our study, individuals receiving ADT had dramatically reduced isometric muscular strength in the lower extremities. The reason for the difference may be the use of different isometric muscle strength measurement methods.

There is only one study in the current literature concerning irisin levels in prostate cancer patients. Aslan et al. (29) found that serum irisin levels of prostate cancer patients were lower (p<0.05). However, in this study, details pertaining to prostate cancer patients were not included. In the current study, plasma irisin levels did not reveal statistically significant differences between any group. However, irisin levels in the ADT group were lower than that in other groups. This finding may suggest lower plasma irisin level tendency following muscle mass and strength loss due to ADT.

Tekin et al. (30) observed that proliferation and cell viability decreased in androgen receptor-positive and androgen receptor-negative prostate cancer cells when they treated these cells with irisin. They suggested that the cytotoxic effect of irisin on prostate cancer cells is independent of the androgen receptor mechanism (30). In addition, irisin yields these effects without affecting non-malignant cells (30,31). In light of these findings, irisin, a myokine released during exercise, can be considered to have a direct effect in preventing the growth and spread of prostate cancer, and be a potential new treatment (14,31,32).

Fassier et al. (22) observed that the IPAQ scores of prostate cancer patients had decreased after diagnosis. In the current study, no significant difference between the groups was found, although the average IPAQ scores were lower in the non-ADT and ADT groups.

Barrére et al. (20) evaluated sarcopenia risks of 52 cancer patients, using the SARC-F scale. The SARC-F scores of two male patients over the age of 80 were ≥4, and they were evaluated as risky regarding sarcopenia (20). In the current study, the ages of participants varied between 54 and 76, and SARC-F scores did not display any significant difference between the groups.

Gagliano-Jucá et al. (33) evaluated the QoL of 37 prostate cancer patients for whom they had planned to administer at least six months of ADT, and 40 prostate cancer patients who were not receiving ADT. They observed that SF-36 and subdomain scores were similar for groups. In the current study, no significant differences could be found, although the physical function and limitation to physical functioning scores of the ADT group were lower.

Köşkderelioğlu et al. (26) found that the FSS scores of patients receiving ADT were higher. In the current study, no statistically significant difference could be found between the groups, although the FSS scores were higher in the ADT group.

To conclude; ADT has negative effects on lower extremity function tests (5TSTS and FRT) and muscle strength (quadriceps and hamstring). Muscle strength and physical functions of patients who are receiving ADT, and who will start receiving ADT should be monitored, and protective measures should be taken. Although there was no difference between the groups in terms of irisin levels in this study, irisin production can be stimulated in future, prospective follow-up exercise studies.

Ethics Committee Approval / Etik Komite Onayı

Suleyman Demirel University, Faculty of Medicine Clinical Research Ethics Committee (approval number: 38, date: 13.02.2020)

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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