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Effect of Body Weight Reduction on Serum Irisin Levels: Experimental Study

Vücut Ağırlığı Azalmasının Serum İrisin Düzeylerine Etkisi: Deneysel Çalışma

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ABSTRACT Objective: We evaluated the effect of body weight reduction on serum irisin levels and analyzed the potential relationships of irisin with anthropometric and laboratory parameters. **Material and Methods:** The study included 42 females with median (2.5-97.5 percentiles) body mass index (BMI) of 38.3±5.5 kg/m^2 who admitted to the obesity department and completed a 32 weeks weight reduction programme. Anthropometric and laboratory parameters were determined at the first intervention (T1) and after 8th and 32nd weeks (T2 and T3). Changes in parameters and relationships among irisin levels were evaluated. A preliminary analysis was also performed by dividing patients as metabolic syndrome positive and negative. **Results:** When compared with T1; BMI, waist and hip circumference, total cholesterol and triglyceride levels were significantly decreased at T2 and T3 (p<0.001) however, there was a significant decrease in body muscle mass, homeostatic model assessment-insulin resistance, HbA1c, and high density lipoprotein cholesterol levels only at T3. There was a significant difference between T1, T2 and T3 for hip circumference and body muscle mass in Kruskal-Wallis analysis (p=0.000 and 0.007 respectively). Although there was no significant change at irisin levels at T2, a significant increase was observed at T3 (p=0.007). There was no correlation between basal irisin levels and the anthropometric and laboratory parameters. There was no significant difference between metabolic syndrome positive and negative patients according to serum irisin levels. **Conclusion:** Body weight reduction caused a significant increase in irisin levels but there was no correlation between basal irisin levels and the anthropometric and laboratory parameters.

Keywords: Obesity, FNDC5 protein; human, insulin resistance, diet therapy

ÖZET Amaç: Bu çalışmada, vücut ağırlığı azalmasının, serum irisin seviyeleri üzerindeki etkisini değerlendirdik ve irisinin, antropometrik ve laboratuvar parametreleri ile potansiyel ilişkisini analiz ettik. **Gereç ve Yöntemler:** Çalışmaya, medyan (2,5-97,5 persentil) beden kitle indeksi (BKİ) 38,3±5,5 kg/m^2 olan ve obezite bölümüne başvurup 32 haftalık zayıflama programını tamamlayan 42 kadın dâhil edildi. Antropometrik ve laboratuvar parametreleri, ilk müdahalede (T1) ve 8 ve 32. haftalarda (T2 ve T3) ölçüldü. Parametrelerdeki değişim ve irisin seviyeleri arasındaki ilişki değerlendirildi. Ayrıca metabolik sendrom pozitif ve negatif hastaları ayırarak ek bir analiz yapıldı. **Bulgular:** T1 ile karşılaştırıldığında; BKİ, bel ve kalça çevresi, total kolesterol ve trigliserid seviyeleri T2 ve T3'de anlamlı olarak azaldı (p<0,001); ancak vücut kas kütlesi, insülin direncinin homeostatik modeli değerlendirmesi, HbA1c ve yüksek yoğunluklu lipoprotein kolesterol seviyelerinde sadece T3'de anlamlı bir azalma oldu. Kruskal-Wallis analizlerinde kalça çevresi ve vücut kas kütlesi açısından T1, T2 ve T3 arasında anlamlı farklılık saptandı (sırasıyla p=0,000 ve 0,007). T2'de irisin seviyelerinde anlamlı bir değişiklik olmamasına rağmen T3'de anlamlı bir artış gözlendi (p=0,007). Bazal irisin seviyeleri ile antropometrik ve laboratuvar parametreleri arasında korelasyon saptanmadı. Metabolik sendrom pozitif ve negatif hastalar arasında serum irisin seviyeleri açısından anlamlı farklılık saptanmadı. **Sonuç:** Vücut ağırlığının azalması, irisin düzeylerinde önemli bir artışa neden oldu, ancak bazal irisin düzeyleri ile değerlendirilen antropometrik ve laboratuvar parametrelerinin hiçbiri arasında ilişki saptanmadı.

Anahtar Kelimeler: Obezite, FNDC5 protein; insan,insülin direnci, diyet terapi

Obesity has reached epidemic proportions in both high-income and many middle-income countries.[1] It causes an increase in mortality and morbidity rates by triggering or worsening various diseases.[2,3] Continuing dysregulation in terms of energy intake and consumption is the essential factor in obesity.[1]

Fat or the digestive tract secrete signals that have an important function in the regulation of body weight.[4] Skeletal muscle and adipose tissue secrete myokines and adipokines respectively and play an important role in sustaining body weight.[5] White adipose tissue (WAT) maintains energy homeostasis by

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accumulating excess energy, while brown adipose tissue (BAT) adjusts body temperature by producing heat and expanding the energy.[6,7] The browning of adipose tissue is valuable in recovering insulin sensitivity and reducing weighting.[8]

Irisin is produced extracellularly at the time of cleavage of fibronectin Type III domain-containing protein 5 (FNDC5) and it is an exercise-mediated myokine. Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha induces its expression but its pathophysiology remains largely unknown.[9] It consists of 112 amino acids and several organs such as the heart, tongue, liver, placenta, pancreas, rectum, ovaries, skeletal system, spleen, stomach, neural system, and WAT are involved in its release. Irisin induces the conversion of WAT to BAT. According to the mice studies over-expression of FDNC5/irisin causes an increase in energy consumption and thermogenesis thus irisin has been suggested to have a promising function in glucose homeostasis, insulin resistance, and obesity.[10,11] Based on this context, it has been quickly suggested that irisin may be useful in the treatment of several pathological conditions characterized by an imbalance in energy demand and expenditure, such as obesity and diabetes.[10,12,13]

It is also shown that irisin is secreted by adipocytes from WAT in rats and humans.[14] Anorectic animals had distinct irisin secretion, while obese animals with higher adipose tissue had higher irisin levels. It is considered that adipose tissue may contribute to circulating irisin levels depending on the physiological or pathological situation.[15] However, data regarding irisin levels in humans and different metabolic conditions are uncertain.[16] Conflicting results were reported about the association of irisin with body mass index (BMI). In some studies, no relationship was observed, while positive or negative relationships have also been reported.[9,17-23] Besides, limited data are available concerning the Turkish population.

We evaluated the effect of body weight reduction on serum irisin levels and analyze the possible associations of irisin with anthropometric and commonly used laboratory parameters in non-diabetic obese patients.

MATERIAL AND METHODS

The study population included 42 females with median (2.5-97.5 percentiles) age of 42.9±12.8 years and BMI of 38.37±5.55 kg/m^2, who were admitted to the Obesity Department of Dr. Lütfi Kırdar City Hospital between April 01, 2019 and April 01, 2020 and a prospective cohort study was conducted. Six women were at postmenopause, 4 were at perimenopause and 3 were at menopause stage. They completed a 32 weeks weight reduction program including a balanced hypocaloric diet containing 55% of the energy supply as carbohydrates, 15% as proteins within a 3-5 meals per day pattern (-30% energy restriction) and regular exercise [minimum of 150 min (2.5 h) of moderate-intensity exercise per week]. The weight reduction program was directed by trained dieticians and an expert in family medicine. Patients with known chronic diseases such as diabetes mellitus, hyperparathyroidism, hypercortisolism, renal insufficiency, chronic liver diseases, and malignancy were excluded. Anthropometric measurements and clinical laboratory measurements [homeostatic model assessment-insulin resistance (HOMA-IR), HbA1c, high density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride, cortisol, creatinine, urea, uric acid, vitamin B_{12}, folate, hemoglobin, albumin, thyroid-stimulating hormone (TSH), and irisin] were determined at the first intervention (1st measurement; T1) and after 8th and 32nd weeks (2nd and 3rd measurements; T2 and T3). Changes in parameters and relationships among serum irisin levels were evaluated. A preliminary analysis was also performed by separating metabolic syndrome positive and negative patients.

Anthropometric measurements and body composition determinations were performed using a bioelectrical impedance analyzer GAIA 359 PLUS (Jawon Medical, Gyeongsan-si, Gyeongsangbuk-do, South Korea). The device can measure height, weight, body fat, and muscle mass. BMI was calculated with the formula; weight (kg)/height^2 (m^2). Samples were collected after a 12 hour overnight fasting and glucose, urea, uric acid, kreatinin, total cholesterol, triglyceride, HDL cholesterol, albumin were analyzed using AU 5800 (Beckman Coulter, Brea,

CA, USA). Insulin was determined using Cobas e-411 (Roche Diagnostics, Mannheim, Germany), vitamin B_{12}, folate, and TSH were analyzed using UnicelDxI 800 (Beckman Coulter, Brea, CA, USA). HOMA-IR is calculated from the formula; fasting serum glucose (mg/dL)xfasting serum insulin (μU/mL)/405. HbA1c was determined using Bio-Rad Variant II Turbo HPLC (USA). The patient's serum was separated and immediately frozen and kept at -80 ºC until analyzed for irisin. Serum irisin concentrations were measured using an ELISA kit (BioVendor-Laboratorni medicina a.s., Brno, Czech Republic). The sensitivity (limit of detection) of the assay declared by the manufacturer is 1 ng/mL. Assay range is 0.001 μg/mL-5 μg/mL, intra-assay coefficient of variation (CV's) are 4.86% and 6.74% for 0.678 μg/mL and 1.539 μg/mL and inter-assay CV's are 9.67% and 9.71% for 0.532 μg/mL and 0.696 μg/mL respectively. The study was conducted following the Declaration of Helsinki Ethical Principles. The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital. Decision date and number: 23.07.2015/89513307/ 1009/474. All participants signed informed consent before enrolment.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the SPSS program (Statistical Package for Social Science, version 11.7; Chicago, IL, USA). The distribution of the parameters was checked by the Kolmogorov-Smirnov test and since the distribution was non-parametric, data were expressed as median (2.5-97.5 percentiles). The comparison of the dependent variables was done with the Mann-Whitney U test. Correlations between clinical and anthropometric variables and the serum irisin levels were determined by Spearman correlation analysis. Kruskal-Wallis test was performed to compare the three measurements. Statistical significance for all tests was set at $p<0.05$.

RESULTS

The anthropometric and laboratory parameters of the patients throughout the program were given in Table 1. When compared with T1; BMI was reduced by 4.2% and 7.3% at T2 and T3 respectively. BMI, waist and hip circumference, total cholesterol, and triglyceride levels were significantly decreased at T2 and T3 (p's<0.001) but there was a significant decrease in body muscle mass, HOMA-IR, HbA1c, and HDL cholesterol levels only at T3. There was a significant difference between T1, T2, and T3 for hip circumference and body muscle mass in Kruskal-Wallis analysis (p=0.000 and 0.007, respectively). Although there was no significant change at irisin levels at T2, a significant increase was observed at T3 (p=0.007). There was no significant correlation between irisin levels at T1, T2 and T3, and the anthropometric and laboratory parameters (Table 2). Correlation coefficients between basal irisin levels and anthropometric and laboratory parameters were shown in Table 3. Fifteen patients were metabolic syndrome positive and 27 patients were negative according to the International Diabetes Federation criteria.[19] There were significant differences for HOMA-IR, triglyceride, and TSH values between metabolic syndrome positive and negative patients (p=0.013, 0.042, and 0.000, respectively), and no significant difference was determined between the two groups according to irisin levels (Table 4).

DISCUSSION

Compared to T1; weight, BMI, waist and hip circumference, total cholesterol, and triglyceride levels were significantly decreased at both T2 and T3 (p<0.001) for all, however, there was a significant decrease in body muscle mass, HOMA-IR, HbA1c, and HDL cholesterol levels only at T3. There was a significant difference between T1, T2, and T3 for hip circumference and body muscle mass in Kruskal-Wallis analysis (p=0.000 and 0.007, respectively). There was no significant change in irisin levels at T2, while a significant increase was observed at T3 (p=0.007).

It has been suggested that the iris acts as a muscle-derived energy expenditure signal and causes browning of adipose tissue and thermogenesis by increasing uncoupling protein 1 levels.[9] This effect may improve the WAT metabolism and increase body energy expenditure, which makes the irisin a potential new target for the treatment of metabolic diseases.[2]

TABLE 1: Anthropometric and laboratory parameters of the patients.

	First week median (2.5-97.5 persentile)	8th week median (2.5-97.5 persentile)	32nd week Median (2.5-97.5 percentile)
Number	42	42	42
Age (years)	42 (18.2-63.4)	42 (18.2-63.4)	42 (18.2-63.4)
Weight (kg)	97.2 (76.9-127.1)	94.0 (72.9-118.4)	90.5 (71.6-113.4)
BMI (kg/m^2)	37.40 (30.69-53.60)	36.58 (29.35-49.81)	35.07 (27.29-47.81)
Waist circumference (cm)	124 (113-145)	120 (110-143)	118 (108-139)
Hip circumference (cm)	113 (90-132)	111 (88-130)	109 (87-128)
Fat mass	40.7 (28.2-58.8)	38.7 (26.6-52.0)	36.6 (25.4-51.3)
Muscle mass	50.8 (41.1-66.5)	50.4 (41.0-66.6)	49.3 (39.5-64.4)
HOMA-IR	4.04 (1.68-13.76)	4.12 (1.57-12.68)	3.79 (1.56-13.09)
HbA1c (%)	5.5 (4.7-6.8)	5.5 (4.6-6.7)	5.4 (4.6-6.9)
HDL cholesterol (mg/dL)	47 (33-70)	49 (32-71)	49 (32-73)
Total cholesterol (mg/dL)	208 (134-327)	200 (130-284)	200 (126-279)
Triglyceride (mg/dL)	146 (47-302)	140 (44-270)	132 (44-266)
Creatinine (mg/dL)	0.68 (0.52-0.93)	0.69 (0.53-0.92)	0.67 (0.51-0.92)
Urea (mg/dL)	27 (15-48)	27 (15-46)	25 (15-46)
Uric acid (mg/dL)	5.5 (4.1-10.5)	5.7 (4.4-10.0)	5.7 (4.3-10.0)
Vitamin B_{12} (pg/mL)	207 (125-404)	220 (136-398)	226 (150-459)
Folate (ng/mL)	7.1 (2.1-15.7)	7.4 (2.3-16.3)	7.8 (2.4-16.5)
Hemoglobine (g/dL)	12.8 (11.1-16.1)	12.9 (11.2-15.7)	12.9 (11.5-16.0)
Albumin (g/dL)	4.45 (3.81-5.34)	4.55 (3.62-7.19)	4.57 (3.85-5.34)
TSH (IU/L)	1.99 (0.41-7.74)	2.15 (0.45-7.89)	1.95 (0.51-7.05)
Irisin (ug/mL)	4.23 (2.67-14.37)	5.02 (2.18-9.94)	5.19 (2.30-12.89)

BMI: Body mass index; HOMA-IR: Homeostatic model assessment-insulin resistance; HDL: High density lipoprotein; TSH: Thyroid-stimulating hormone.

Recent studies on the possible beneficial effect of irisin on the treatment of obesity are conflicting, as unexpectedly high levels of irisin have been observed in obese animals and humans, and weight regains and the onset of insulin resistance.[14,16,19]

There is no general agreement on serum irisin levels and their correlation with BMI.[4,15] Stengel et al. and Pardo et al. both showed a positive correlation between serum irisin levels and BMI.[4,19] Morbid obese patients showed higher irisin levels and according to Pardo et al., fat mass was the main contributing factor for high irisin levels in obesity. Stengel et al. concluded that irisin increases as a physiological adaptation to improve glucose tolerance which is impaired in obese individuals. Other studies are reporting a positive correlation between irisin levels and BMI.[16,21,23]

However in a study by Moreno-Navarrete et al. including non-diabetic subjects with a BMI of 27.61±3.8, a negative association was observed between serum irisin levels and BMI, fat mass percent, and waist-to-hip ratio.[20] In another study conducted with normal glucose tolerance and new-onset Type II diabetes mellitus patients, irisin was also found to be negatively correlated with BMI.[24]

Similar to the study by Sanchis-Gomar et al., we didn't find any correlation between circulating irisin levels and any anthropometric or laboratory parameters.[18] In their study, they did not examine the correlation of irisin with fat or muscle mass and explained this as a limitation of their study.

Studies about plasma irisin levels were performed on varying patient groups and various results were reported. Several studies reported associations between plasma irisin levels and metabolic factors in non-diabetics, but not in subjects with Type II diabetes mellitus.[24,25] Our study group included 42 non-diabetic subjects and 15 of them were diag-

TABLE 2: Differencs between repeated measures for anthropometric and laboratory parameters.

	T1 vs T2 (p)	T2 vs T3 (p)	T1 vs T3 (p)	Kruskal-Wallis p
BMI (kg/m^2)	*<0.001	*<0.001	*<0.001	0.054
Waist circumference	*<0.001	*<0.001	*<0.001	*0.001
Hip circumference	*<0.001	*<0.001	*<0.001	*0.007
Body fat mass	*0.001	*<0.001	*0.001	0.104
Body muscle mass	0.287	*0.001	*0.001	0.285
HOMA-IR	0.113	0.030	*0.013	0.431
HbA1c (%)	0.856	*0.015	*0.025	0.164
HDL cholesterol	0.827	0.109	*0.022	0.739
Total cholesterol	*0.001	0.383	*0.001	0.392
Triglyceride (mg/dL)	*0.002	0.523	*0.003	0.716
Cortisol	0.452	0.065	*0.016	0.393
Creatinine (mg/dL)	0.994	0.537	0.518	0.970
Urea	0.871	0.927	0.676	0.895
Uric acid	0.398	0.338	1.000	0.818
Vitamin B12	0.009	0.008	0.009	0.336
Folate	0.055	0.160	0.035	0.838
Hemoglobine	0.090	0.310	0.101	0.642
Albumin	0.070	0.805	*0.005	0.276
TSH	0.066	0.867	0.252	0.896
Irisin	0.314	0.200	*0.007	0.077

*Significant difference; p<0.05; BMI: Body mass index; HOMA-IR: Homeostatic model assessment-insulin resistance; HDL: High density lipoprotein; TSH: Thyroid-stimulating hormone.

nosed with metabolic syndrome and 27 patients were not, and no significant difference was observed between groups.

There are also no consistent results about the impact of weight reduction on irisin levels in obese individuals. In a study by Fukushima et al., irisin levels didn't change significantly after the diet program. Otherwise, a significant improvement was observed on body fat percentage, subcutaneous fat area, triglycerides, and fasting blood glucose levels whose irisin levels were elevated after the weight loss.[26] In a study by Lopez-Legarrea et al., it has been shown that irisin is decreased after the weight loss program since it is needed less to improve the altered metabolism.[27] Similarly, in the study of Crujeiras et al., a significant decrease was observed in the irisin levels after the hypocaloric diet programme and they concluded that irisin levels demonstrated the body fat mass and that irisin levels were modified according to the adiposity level of the body.[23] Conversely, we found a significant increase in irisin levels at 32nd weeks.

TABLE 3: Correlation of basal irisin with anthropometric and laboratory parameters.

	r value	p value
Age	-0.145	0.353
Weight	0.088	0.573
BMI (kg/m^2)	0.205	0.189
Waist circumference	0.107	0.493
Hip circumference	0.243	0.119
Body fat mass	0.178	0.253
Body muscle mass	-0.063	0.685
HOMA-IR	0.220	0.159
HbA1c	0.292	0.061
HDL cholesterol	-0.087	0.578
Total cholesterol	0.079	0.929
Triglyceride	-0.055	0.726
TSH	0.031	0.841

Correlation is significant at the p<0.05 level; BMI: Body mass index; HOMA-IR: Homeostatic model assessment-insulin resistance; HDL: High density lipoprotein; TSH: Thyroid-stimulating hormone.

Besides, inadequate specificity of the irisin ELISA kits, inter-population or methodological vari-

TABLE 4: Anthropometric and laboratory parameters of patients with and without metabolic syndrome.

	Patients with metabolic syndrome n=15			Patients without metabolic syndrome n=27			
	T1	T2	T3	T1	T2	T3	p value
Age (years)	39 (20-62)			42 (19-65)			0.883
Weight (kg)	101 (77-134)	97 (75-120)	95 (72-111)	93 (77-120)	90 (71-115)	85 (71-115)	0.364
BMI (kg/m^2)	40 (31-54)	38 (28-49)	38 (27-45)	36 (30-52)	36 (30-50)	33 (27-50)	0.146
Waist circumference (cm)	114 (98-133)	111 (97-130)	109 (95-129)	112 (83-132)	110 (82-129)	109 (82-126)	0.324
Hip circumference (cm)	130 (114-143)	127 (112-139)	120 (110-135)	122 (113-147)	120 (110-144)	117 (106-139)	0.574
HOMA-IR	5.4 (3.0-18.8)	5.4 (2.8-17.4)	4.5 (2.2-17.0)	3.6 (1.6-8.4)	3.6 (1.5-6.2)	3.5 (1.5-6.1)	*0.013
HbA1c (%)	5.7 (5.1-6.9)	5.6 (5.2-7.0)	5.4 (4.9-7.1)	5.5 (4.7-6.6)	5.5 (4.3-6.4)	5.3 (4.5-6.6)	0.093
TSH (IU/L)	1.5 (0.8-3.9)	1.6 (0.8-3.9)	1.7 (0.8-5.4)	2.3 (0.2-8.5)	2.6 (0.2-8.5)	2.1 (0.5-7.5)	*0.042
HDL cholesterol (mg/dL)	42 (33-67)	40 (30-65)	44 (30-64)	51 (35-70)	50 (34-74)	52 (34-71)	0.124
Total cholesterol (mg/dL)	217 (153-249)	215 (150-251)	200 (130-238)	206 (127-335)	199 (123-279)	200 (123-279)	0.744
Trigliserid (mg/dL)	214 (159-322)	201 (140-270)	172 (80-280)	117 (38-244)	120 (35-226)	119 (39-253)	*0.000
Creatinine (mg/dL)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.6-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.820
Urea (mg/dL)	25 (17-49)	25 (16-45)	25 (16-47)	27 (14-48)	27 (15-47)	27 (15-44)	0.388
Uric acid (mg/dL)	5.6 (4.6-9.9)	5.6 (4.7-9.8)	6.2 (4.6-10.0)	5.5 (4.1-10.6)	5.7 (4.3-9.8)	5.6 (4.2-9.9)	0.861
B_{12} (pg/mL)	199 (130-374)	220 (140-370)	210 (170-372)	222 (123-416)	221 (134-413)	240 (150-467)	0.565
Hemoglobine (g/dL)	12 (11.1-13.6)	12 (11.1-14.6)	12 (11.4-13.8)	13 (11.1-16.7)	13 (11.7-16.4)	13 (12.0-16.6)	0.103
Irisin	4.26 (2.95-7.16)	4.88 (2.81-9.85)	6.35 (3.68-11.70)	4.19 (2.53-15.92)	5.16 (1.97-10.00)	4.54 (1.73-13.30)	0.261

*Significant difference; p<0.05; BMI: Body mass index; HOMA-IR: Homeostatic model assessment-insulin resistance; TSH: Thyroid-stimulating hormone; HDL: High density lipoprotein.

ations of the studies might be the reason for the discrepancy between the reported results.[18,28] In the literature, 5 different irisin assays have been reported and the level of serum and plasma irisin levels changed from 1 to 2,000 ng/mL according to the analytical sensitivity and spesificıty of these assays. The presence of different protein fragments or free or complex protein forms in the samples, protein glycosylation, and cross-reactivity may explain the variability in the results of immunologic tests which makes the comparison of the studies difficult.[29] We used the BioVendor ELISA kit with an assay range of 0.001-5 µg/mL in the present study.

Further researches are needed to clarify the role of irisin in different metabolic conditions, deficiency in weight loss or relapse after nutritional intervention or bariatric surgery. In the future, irisin may contribute to obesity and accompanying diseases.

In this longitudinally designed study, we evaluated changes in anthropometric and biochemical parameters related to metabolic profile in parallel with irisin levels. A possible limitation is the study group consisted of women only, which limits the evaluation of the gender effect.

CONCLUSION

Body weight reduction caused a significant increase in irisin levels but there was no correlation between basal irisin levels and the anthropometric and laboratory parameters.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Özlem Çakır Madenci, Müjgan Kaya Tuna, Özlem Hürmeydan;* ***Design:*** *Özlem Çakır Madenci, Müjgan Kaya Tuna, Özlem Hürmeydan, Asuman Orçun;* ***Control/Supervision:*** *Özlem Çakır Madenci, Özlem Hürmeydan;* ***Data Collection and/or Processing:*** *Özlem Çakır Madenci, Müjgan Kaya Tuna, Özlem Hürmeydan;* ***Analysis and/or Interpretation:*** *Özlem Çakır Madenci, Asuman Orçun;* ***Literature Review:*** *Özlem Çakır Madenci, Özlem Hürmeydan, Müjgan Kaya Tuna, Asuman Orçun;* ***Writing the Article:*** *Özlem Çakır Madenci, Özlem Hürmeydan;* ***Critical Review:*** *Özlem Çakır Madenci, Asuman Orçun;* ***References and Fundings:*** *Özlem Çakır Madenci, Müjgan Kaya Tuna, Asuman Orçun;* ***Materials:*** *Müjgan Kaya Tuna, Özlem Çakır Madenci.*

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