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Serum Irisin Levels in Cigarette Smokers

Sigara İçenlerde Serum İrisin Düzeyleri

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Abstract

Objective: Irisin, a newly discovered myokine, increases thermogenesis and energy consumption, especially after exercise. It has also been reported to stimulate the transformation of white fat cells into brown fat cells. Thus, it causes weight loss and increases the sensitivity to insulin. Nicotine affects the energy metabolism of the body through several mechanisms. Cigarette smokers are widely known to show decreased weight gain and increased weight loss. Since irisin and smoking/nicotine have similar effects on energy metabolism, this study proposed to determine the serum irisin levels in smokers. **Material and Methods:** Thirty-one healthy smokers aged 17-24 years and 31 age-matched healthy non-smokers were included in this study. Serum irisin levels were determined using ELISA. **Results:** The smokers had been smoking for an average of 31±19 (2-84) months and smoked an average of 13.7±0.4 (5-25) cigarettes daily. The smokers had higher height and body weight and levels of serum creatinine and triglyceride and lower levels of HDL-C than non-smokers ($p<0.05$). Serum irisin levels and body mass index were not different between the two groups ($p>0.05$). The serum irisin level was correlated only with serum creatinine level in the entire group ($r=-0.26$, $p<0.05$). The serum irisin levels were not correlated with the duration and amount of cigarette smoking, as well as levels of serum glucose, insulin, total cholesterol, triglyceride, LDL-C, HDL-C, alanine aminotransferase, free T4, and TSH in the entire group ($p>0.05$). **Conclusion:** Serum irisin level in cigarette smokers is not different to that of non-smokers. It is not related to the duration and amount of cigarette smoking. Further prospective dose and time-controlled studies are needed to investigate whether similar effects of smoking/nicotine exposure on energy metabolism are related to irisin metabolism.

Keywords: Cigarette; smoking; irisin; body weight; body mass index

Özet

Amaç: İrisin, özellikle egzersizden sonra termogenezisi ve enerji harcanmasını artıran yeni tanımlanmış bir miyokindir. Aynı zamanda beyaz yağ dokusu hücrelerine, kahverengi yağ dokusu hücresi özellikleri kazandırdığı rapor edilmiştir. Böylece kilo kaybına neden olur ve insülin duyarlılığının artışına neden olur. Nikotin, pek çok değişik mekanizma ile vücut enerji metabolizmasını etkilemektedir. Sigara içenlerde kilo alımının azaldığı ve kilo kaybının arttığı yaygın olarak bilinmektedir. İrisin ve sigara içiminin/nikotinin enerji metabolizmasında benzer etkileri olduğu görüldüğü için bu çalışmada sigara içenlerde serum irisin düzeylerinin tayini planlanmıştır. **Gereç ve Yöntemler:** Bu çalışmaya, yaşları 17-24 yıl arasında değişen 31 sağlıklı, sigara içen birey ile yaş açısından benzer 31 sağlıklı, sigara içmeyen birey dâhil edildi. Serum irisin düzeyleri ELISA yöntemi ile tayin edildi. **Bulgular:** Sigara içenlerde sigara içimi süresi ortalama 31±19 (2-84) ay ve içilen sigara adedi ortalama 13,7±0,4 (5-25) idi. Sigara içen bireylerin boy uzunluğu, vücut ağırlığı, serum kreatinin, trigliserid düzeyleri sigara içmeyenlerden yüksek iken, HDL-K düzeyleri daha düşük idi ($p<0,05$). Sigara içenlerin serum irisin düzeyleri ve beden kitle indeksi, sigara içmeyenlerden farklı değildi ($p>0,05$). Serum irisin düzeyleri, sadece tüm çalışma grubunda serum kreatinin düzeyleri ile korele idi ($r=-0,26$, $p<0,05$). Serum irisin düzeyleri ile sigara içim süresi, sigara miktarı, serum glukoz, insülin, total kolesterol, trigliserid, LDL-K, HDL-K, alanin transaminaz, serbest T4 ve TSH düzeyleri arasında bir korelasyon saptanmadı ($p>0,05$). **Sonuç:** Sigara içenlerde serum irisin düzeyleri, sigara içmeyenlerden farklı değildir. Serum irisin düzeyleri, sigara içiminin süresi ve miktarıyla ilişkili değildir. Sigara içiminin enerji metabolizmasındaki benzer etkilerinin, irisin metabolizmasıyla ilişkili olup olmadığı ileriye dönük, doz ve zaman kontrollü çalışmalarla araştırılmalıdır.

Anahtar kelimeler: Sigara içimi; irisin; vücut ağırlığı; beden kitle indeksi

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Introduction

The origin and histological structure of brown adipose tissue (BAT) varies from that of white adipose tissue (WAT). BAT, known to mainly exist in the body during the neonatal period, has been reported in the supraclavicular, paravertebral, mediastinal, and peri-renal regions during adulthood (1-3). In BAT, non-shivering thermogenesis and energy expenditure occur through ATP synthesis by oxidative phosphorylation via the uncoupling protein 1 (UCP1), present in the inner membrane of the mitochondria of BAT cells (4).

The WAT, located in the visceral and subcutaneous tissue, has different functions from BAT and acts as a store of adipose tissue in the body. Some pharmacological stimuli have been shown to induce UCP1 transcription in WAT cells and confer thermogenetic BAT cell properties (browning) to these cells; thus, achieving good metabolic effects (1). One of these stimuli is irisin (1,2,5,6). Irisin is a myokine that was recently described in 2012 by Boström et al. (5). It is a protein that is a cleaved and secreted fragment of FNDC5, a membrane protein found in mouse and human plasma (5). Irisin has been reported to stimulate the transformation of WAT cells into BAT cells and increase the expression of metabolic genes through UCP1, which is especially stimulated after exercise (4-6). Irisin has also been documented to increase thermogenesis, oxidative metabolism, total body energy expenditure, glucose tolerance, as well as cause weight loss and improve insulin resistance (2,6-10). Due to its effects on energy metabolism, the serum irisin levels are monitored in obese and diabetic patients. Conflicting results have been reported in this regard (8). Irisin has also been recommended for use in the treatment of these pathological conditions (6,7).

It has been hypothesized that nicotine may also induce the transformation of WAT into BAT (1,2,10-12). The role of nicotine in BAT metabolism has been investigated previously. The activity of UCP1 is stimulated when BAT is activated by the sympathetic nervous system (4). Acute and chronic smoking have been demonstrated to increase thermogenesis by stimulating the sympathetic system in BAT (4,10-12). On the other hand, the effects of smoking on energy metabolism are also well known. In humans, nicotine consumption through smoking is the main agent that affects energy metabolism. It has been documented that food intake and body weight (BW) are reduced in cigarette smokers with the amount of smoking. In contrast, appetite and weight gain increase after quitting smoking. Another effect of cigarette smoking/nicotine consumption is that it increases the visceral fat content and insulin resistance by changing the distribution of body fat without changing the amount of total body fat tissue in direct proportion to the dose. It has been reported that cigarette smoking is associated with the development of Type 2 diabetes and metabolic syndrome. Moreover, it was observed that insulin sensitivity improved after stopping smoking (4,13,14). Thus, the metabolic effects of cigarette smoking or nicotine intake on energy metabolism appear to be similar to those of irisin. In some animal studies, the effects of nicotine intake on both UCP proteins and WAT/BAT have been investigated, with contradictory results (10,11).

To the best of our knowledge, none of the existing studies in the literature have investigated serum irisin levels in cigarette smokers. In this study, it was planned to investigate whether smoking and serum irisin levels were related, and to contribute to the issue of smoking and obesity, which are common public health problems.

Material and Methods

The study group consisted of students of the Eskişehir Osmangazi University and workers in the Hospital of Eskişehir Osmangazi University Faculty of Medicine. Thirty-one healthy cigarette smokers (8 female, 23 male) aged between 17-24 yrs were included in this study. The control group consisted of 31 healthy non-smokers (17 female, 14 male) who had a similar age range as the smokers.

Subjects with any known chronic disease and undergoing any drug treatment were not included in the study. After laboratory analysis, those who were detected with impaired fasting glucose, elevated alanine aminotransferase (ALT) levels, and subclinical hypothyroidism were also excluded from the study.

All smokers were inquired about the duration of cigarette smoking, and the number of cigarettes smoked in a day.

The study protocol was approved by the local Ethics Committee of Eskişehir Osmangazi University. The study was carried out per the Declaration of Helsinki (Helsinki Declaration, revised 2013). Written informed consent was obtained from all the participants.

The body weights (kg) and heights (m) of all the participants were measured, and the body mass index (BMI) (kg/m^2) was calculated.

After overnight fasting, venous blood samples were collected from all the participants. Levels of serum glucose, total cholesterol, triglycerides (TG), low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, Alanine Aminotransferase (ALT), free T4, and thyroid-stimulating hormone (TSH) were determined by photometry using the Roche Cobas 8,000 analyzer c702 module (Roche Diagnostics GmbH, Penzburg, Germany). Insulin levels were determined by the electrochemiluminescence immunoassay using the Roche Cobas 8,000 c602 (Roche Diagnostics GmbH, Penzburg, Germany) autoanalyzer.

Serum samples from the venous blood, which were aliquoted for determining the irisin levels, were stored at -80 °C until further analysis. Serum irisin levels were measured using a commercially available ELISA kit (RAG018R, BioVendor Inc., Candler, NC, USA) on the VICTOR X3 analyzer (PerkinElmer, USA) at the Biochemistry Laboratory in our hospital. The sensitivity of the method was 1 ng/mL, while the intra-assay and inter-assay CVs were <8.2% and <9.7%, respectively.

Statistical Analysis

The statistical package SPSS version 26.0 was used for the statistical analysis. For the comparisons between groups, the independent samples t-test and Mann-Whitney U test were used. The correlation was analyzed using the analysis of Spearman's correlation. p value of <0.05 was considered to be statistically significant.

Results

The clinical characteristics of the study groups are presented in Table 1, and laboratory results are summarized in Table 2. Serum irisin levels and BMI, did not significantly differ between smokers and non-smokers (p>0.05). It was observed that BW, height, TG, and creatinine levels of the smokers were high, and HDL-C levels were low (p<0.05). Serum irisin level was negatively correlated with only the serum creatinine levels (r=-0.26, p<0.05). The serum irisin levels were not correlated with the duration and amount of smoking, height, BW, BMI, and other investigated parameters in the entire study group, as well as separately in the smoker and the non-smoker groups (p>0.05).

Serum irisin levels did not differ according to gender (median=7.36 (5.78-16) µg/mL in women and 6.39 (5.77-7.12) µg/mL in men) in the entire group (p=0.32), as well as separately in the smoking (median=6.43 (5.44-7.39) µg/mL in women and 6.62 (6.04-6.9) µg/mL in men) (p=0.7) and the non-smoking group (median=8.45 (5.97-17) µg/mL in women and 5.85 (5-9.9) µg/mL in men) (p=0.2).

Table 1. Clinical features of the study groups.

	Smokers (n)	Non-smokers (n)	p value
F/M	8/23	17/24	
Age (month)	237±20 (209-288)	243±18 (204-288)	0.25
BW (kg)	72±13 (45-95)	64±11 (46-92)	0.02
Height (cm)	174±8 (153-186)	170±8 (152-185)>	0.046
Body mass index (kg/m^2)	23.4±3.6 (17-32)	22±2.5 (17-22)	0.789
Duration of smoking (month)	31±19 (2-84)		
Number of cigarettes smoked daily	13.7±0.4 (5-25)		

Table 2. Results of the laboratory analysis.*

	Smokers	Non-smokers	p value
Irisin (µg/mL)	6.61 (5.9-7.1)	6.65 (5.6-15.3)	0.799
Glucose (mg/dL)	82±7.2	84±9	0.61
Insulin (mIU/mL)	10 (7.6-16)	9 (7.5-11)	0.3
Creatinine (mg/dL)	0.8±0.13	0.74±0.14	0.002
ALT (U/L)	16 (11-30)	13 (9-21)	0.79
Free T4 (ng/dL)	1.3±0.15	1.3±0.15	0.61
TSH (mIU/L)	1.86 (1.48-2.63)	2 (1.3-3.1)	0.61
Total cholesterol (mg/dL)	143 (130-164)	147 (129-176)	1.00
LDL-C (mg/dL)	89 (77-119)	89 (71-101)	1.00
HDL-C (mg/dL)	47 (36-59)	55 (46-64)	0.042
Triglyceride (mg/dL)	96 (61-113)	62 (49-91)	0.042

ALT: Alanine transaminase; TSH: Thyroid-stimulating hormone; LDL-C: Low-density lipoprotein-cholesterol; HDL-C: High-density lipoprotein-cholesterol.
*Normal- and not normally distributed data were shown with mean±standard deviation and median (25-75 p), respectively.

Discussion

It is widely known that there is a decrease in weight gain and an increase in weight loss in smokers, whereas weight gain increases after quitting smoking. Nicotine reduces appetite and calorie intake and increases energy expenditure, which explains the reduction in weight gain in smokers (4,13,14). Moreover, it has been demonstrated that nicotine causes weight loss through its lipolytic effect on WAT (4).

It has been reported that this effect of smoking is related to the degree of smoking. While a decrease in BW is observed in both light and moderate smokers, heavy smokers and chronic smokers are overweight and obese, develop insulin resistance, and increased central adiposity (13,14).

In our study, the smokers were taller and heavier than non-smokers. Rather, these individuals had more appropriate BW for their height than simply being heavier than non-smokers. This also suggests that smoking did not induce weight loss and/or decrease weight gain in our study group, which may be related to the relatively shorter duration of smoking.

Irisin, a newly discovered myokine, stimulates the transformation of WAT cells into BAT cells and increases the expression of metabolic genes through UCP1, especially after exercise (4-6). Thus, it increases thermogenesis, oxidative metabolism, total body energy expenditure, and glucose tolerance and induces weight loss and improvement in insulin resistance (2,6-10). In this study, serum irisin levels in smokers were determined because of the possible link between smoking and irisin metabolism, as have been suggested to have similar effects on energy metabolism. In our study, serum irisin levels among smokers were not different from those among non-smokers. The serum irisin levels were not associated with the duration or amount of smoking either. This result suggested that irisin may not be related to smoking, and this hypothesis should be re-investigated with another study model.

It has been observed that irisin levels increase in obese individuals. In several studies, irisin levels are positively correlated with BW, BMI, amount of adipose tissue, and muscle mass, and decrease with weight loss (8). In our study on non-obese individuals, serum irisin levels were not correlated with BW and BMI.

Before the discovery of the irisin, it has been investigated using animal models whether nicotine has a browning effect on WAT in animals exposed to different doses of nicotine for different durations. Some studies have also investigated the effect of nicotine on UCP proteins involved in irisin metabolism (1,2,4,10-12). Acute and chronic smoking

has been demonstrated to increase thermogenesis by stimulating the sympathetic system in BAT (4,10-12). Chen et al. demonstrated in mice exposed to smoking for four days that food intake decreased significantly from the first day of smoking and that weight loss occurred with a decrease in the BAT and retroperitoneal adipose tissue from the second day of smoking. In this study, it was also observed that plasma leptin levels decreased, neuropeptide Y concentrations remained unchanged in the sub-hypothalamic regions, while the UCP1 mRNA expression decreased in WAT and remained unchanged in BAT. Based on these results, these researchers suggested that thermogenesis was not affected by nicotine exposure over a short time. However, in this study, the mRNA expression of UCP3, which is homologous to UCP1, was increased in BAT. The results suggested that lipid utilization and energy expenditure were upregulated with the increase of UCP3 protein, which is known to affect basal metabolism by participating in mitochondrial fatty acid transport in mice exposed to smoking. Thus, smoking may have contributed to the loss of weight and adipose tissue (10).

Yoshida et al. observed that appetite, amount of retroperitoneal and subcutaneous WAT, and BW decreased in obese mice injected with nicotine for six months. Moreover, the protein and mRNA of UCP1 were activated in both BAT and WAT. The researchers demonstrated that features of BAT developed in WAT as observed by immunohistochemical examination, indicating that nicotine caused browning (11).

Arai et al. reported that after 14 days of nicotine injection in rats, the plasma leptin levels, leptin mRNA expression in the omentum, epididymal, and retroperitoneal adipose tissues, and UCP1 mRNA expression in BAT were higher than that in mice which did not receive nicotine. Although the calorific intake of rats decreased on the sixth day of nicotine intake, it was observed that there was no change in either calorific intake or BW after 14 days. In this study, it was observed that continuous nicotine infusion stimulated mRNA expression of UCP1 in BAT regardless of leptin. However, increased UCP1 mRNA expression was not related to the decrease in BW gain in this study (12).

The studies mentioned above suggested that nicotine treatment had similar effects on BAT and UCP1 protein as irisin. However, no study in the literature has investigated the relationship between irisin and smoking or nicotine intake.

Since UCP proteins that mediate the metabolic effects of the irisin were not determined in our study, it is not possible to comment or make a connection regarding this. Moreover, serum irisin levels were not observed to be associated with smoking in this study. On the other hand, in the above-mentioned animal studies, contrasting results were obtained on UCP1 proteins and adipose tissue with exposure to different doses of nicotine for different durations (4,10-12). Similarly, there may be a threshold for the effect of nicotine on irisin in terms of duration, dose, or other factors that have not been investigated in our study. Dose and time-controlled, detailed prospective studies should be conducted on smokers to further investigate this possibility.

In our study, high triglyceride and low HDL-C levels were observed in smokers, which was in line with the atherogenic lipid profile. Serum irisin levels were negatively correlated only with serum creatinine levels. This finding indicates that the kidneys may play a role in the metabolism of irisin.

Contrasting results have been reported regarding the relationship of circulating irisin levels according to gender (5-18). In one study, circulating irisin levels in young adults were not different between the two sexes; however, when lean body mass was adjusted, the levels were observed to be lower in men (15). Circulating irisin levels were lower in adult males with prediabetes (16). On the other hand, it has been reported that in obese children and adolescents, circulating irisin levels did not differ between genders; in the normal BW group, higher irisin levels were observed in girls than in boys (17). Zügel et al. demonstrated that during rest, circulating irisin levels were not different between the two sexes in both of subjects either obese or normal BW and increased significantly in women with normal BW after aerobic exercise (18). Obese subjects had higher irisin concentrations at rest than lean subjects and there was no significant change in irisin concentrations in

neither obese women or men after exercise. These studies indicate that variation in circulating irisin levels according to gender may be affected by factors such as adiposity and exercise.

In our study, the median serum irisin level in the non-smoking group was lower in men than in women, but the difference was not statistically significant. The fact that serum irisin levels were similar between genders in the smoking group may indicate a change in irisin levels with smoking that may nullify the difference in irisin levels between the two sexes. However, in our study, the number of participants was low, and the distribution by gender in the groups was not uniform. This trend in irisin levels between the two sexes was also observed in the non-smoker group. This issue should be investigated further in a larger study.

The limitations of our study are that is the study was a cross-sectional one, the sample size was small, and the participants were light smokers who had just started smoking, due to which the duration of smoking was short.

In conclusion, serum irisin levels in smokers are not different from those of non-smokers. Serum irisin levels are not associated with the duration and degree of smoking and anthropometric parameters. It would be useful to conduct more comprehensive, dose and time-controlled, prospective studies to determine whether there is a link between smoking and irisin metabolism.

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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: Birgül Kırel; Design: Birgül Kırel; Control/Supervision: Birgül Kırel; Data Collection and/or Processing: Birgül Kırel; Analysis and/or Interpretation: İbrahim Özkan Alataş, Birgül Kırel; Literature Review: Birgül Kırel; Writing the Article: Birgül Kırel; Critical Review: Birgül Kırel; References and Fundings: Birgül Kırel; Materials:Birgül Kırel.

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