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ORIGINAL ARTICLE

Are levels of adipokines and micronutrients different in male adult smokers and non-smokers? A case–control study

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KEYWORDS
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Abstract
Objective: Smoking is a common public problem leading to increases in oxidative stress and decreases in the levels of some micronutrients, finally affecting adipokine levels. The aim of this study was to compare the serum levels of omentin (intelectin-1), chemerin, TNF-α, and some micronutrient intakes in male smokers and non-smokers.
Methods: 40 male smokers and 40 male non-smokers with a mean age of 38.6 ± 14.1 years were included in this study. Serum levels of omentin, chemerin, and TNF-α were measured. To calculate the daily intake of energy, carbohydrate, protein, fat, and some of the micronutrients, the 24-h recall and semi-quantitative food frequency questionnaire (FFQ) was used.

Abbreviations: TNF-α, tumour necrosis factor alpha; HIF-1, hypoxia-inducible factor-1; T2DM, type 2 diabetes mellitus; BMI, body mass index; IL-6, interleukin 6; ELISA, enzyme-linked immunosorbent assay; PPAR-γ, peroxisome proliferator-activated receptor gamma.

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Results: Omentin, chemerin, and TNF-α levels in male smokers were lower than non-smokers, but these differences were not statistically significant. However, after adjustment for total and saturated fat intakes and age, omentin ($\beta = 138.4$, $p = 0.027$) and TNF-α ($\beta = 144.5$, $p = 0.015$) revealed significant differences.
Conclusion: The serum levels of omentin, chemerin, TNF-α, and some micronutrient intakes were not significantly different between smokers and non-smokers. Further population studies are needed to clarify this subject.

PALABRAS CLAVE
De fumar;
Adipokines;
Micronutrientes;
Omentin;
Chemerin

Son diferentes los niveles de adipocinas y micronutrientes en hombres adultos fumadores y no fumadores? Un estudio de casos y controles

Resumen
Introducción: El tabaquismo es un problema público común que aumenta el estrés oxidativo y disminuye los niveles de algunos micronutrientes y finalmente afecta los niveles de adipocinas. El objetivo de este estudio fue comparar los niveles séricos de omentina (intelectina-1), quemerina, TNF-α y algunas ingestas de micronutrientes en hombres fumadores y no fumadores.
Metodología: En este estudio se incluyeron 40 hombres fumadores y 40 hombres no fumadores con una edad media de 38,6 ± 14,1 años. Se midieron los niveles séricos de omentina, quemerina y TNF-α. Para calcular la ingesta diaria de energía, carbohidratos, proteínas, grasas y algunos de los micronutrientes se utilizó el cuestionario recordatorio de 24 horas y frecuencia alimentaria semicuantitativa (FFQ).
Resultados: Los niveles de omentina, quemerina y TNF-α en los hombres fumadores fueron más bajos que en los no fumadores, sin embargo, estas diferencias no fueron estadísticamente significativas. Aunque después del ajuste por la ingesta de grasas totales y saturadas y la edad, omentin (β = 138.4, P = 0.027) y TNF-α (β = 144.5, P = 0.015) revelaron diferencias significativas.
Conclusión: Los niveles séricos de omentina, quemerina, TNF-α y algunas ingestas de micronutrientes no fueron significativamente diferentes entre fumadores y no fumadores. Se necesitan más estudios de población para aclarar este tema.

Introduction

Cigarette smoking is the largest preventable cause of death and disability in developed countries. Smoking in low and middle income countries is increasing rapidly; nowadays, the prevalence of smoking among males in populous Asian countries is far higher than in western countries.[1] Studies have found a relationship between cigarette smoking and coronary artery disease, cancer, and stroke. Also smoking causes 3 million deaths per year worldwide.[2] Cigarette smoking causes hypoxia and leads to an increase in the hypoxia-sensitive transcription factor.[3] Hypoxia causes increased IL-6, leptin, and macrophage migratory inhibition factor production and leads to a reduction in adiponectin synthesis and also reduced adiponectin and haptoglobin mRNA levels.[4]

Omentin as a novel adipokine was identified in 2005 and is coded by two genes that have 313 amino acids and KD38-40 molecular weight secreted by visceral adipose tissue, encoded by two genes[5] and it is also expressed in the lungs, heart, placenta, and ovary.[6] Studies have shown that omentin has an effect on weight loss, insulin sensitivity, and type 2 diabetes.[6] Omentin plays a role in regulating insulin sensitivity and it has protective properties. It induces vasodilation and inhibits angiogenesis and inflammation of the blood vessels. Reduced serum omentin levels are associated with increased insulin resistance and it directly induces endothelium-dependent vasodilation and mediates the production of nitric oxide (NO) in the endothelium. Also, omentin reduces inflammatory cytokines.[7]

Chemerin is an adipokine that is mainly expressed in the adipose tissue and liver.[8] Chemerin is secreted as an inactive precursor protein by adipose tissue and it becomes active after separation of the C-peptide and regulates adipocyte differentiation, inducing the cellular expression of inflammatory cytokines, and regulating the expression of adipocyte genes involved in glucose and lipid homeostasis.[9] Studies have shown that chemerin is correlated with ischaemic heart disease and coronary artery disease and inflammation in T2DM patients. Chemerin increases angiogenesis and cell vital routes as well as the uptake of glucose in fat cells, and reduces blood vessel inflammation.[10]

Tumour necrosis factor-alpha (TNF-α) is an inflammatory cytokine that is essentially produced by macrophages, monocytes, adipocytes and skeletal muscles.[11] TNF-α has a positive relationship with obesity and hyperinsulinaemia.[12]

Studies have shown that smoking significantly increases oxidative stress and decreases the levels of vitamins C and E. It is suggested that smokers need to take additional amounts of vitamin E and C in order to avoid the deleterious effects of smoking on their health.[13] Several nutrients exert modulatory effects in multiple levels including gene expression, cell signalling, and protein or adipokine secretion.[14] In this context, vitamin E intervention increased the expression of leptin and adiponectin.[15] Also, supplementation with vitamins E and C increases adiponectin levels and moderately reduced HOMA values, and Intercellular Adhesion Molecule 1 (ICAM-1) and sE-selectin levels in overweight young adults.[16] One study indicated while the serum level of omentin in non-patients smokers was higher than in healthy non-smokers, the serum omentin level in smokers affiliated with lung cancer was lower compared with none patients smokers.[17] This issue can be considered a risk factor in the prognosis of lung cancer in smokers.[17] In another study, there was no significant relationship between current smokers and ex-smokers as regards to plasma chemerin level. Also, one study showed that smoking reduced the response to anti-TNF treatment.[18]

Because a significant part of the general population over 15 years of age, and one fifth of Iranian male adults smoke,[19] in this study male adults were selected.

According to the result of previous studies, in the present study we intended to compare the serum levels of omentin, chemerin, and TNF-α and some of the micronutrient intakes including macronutrients and vitamin E, C and selenium in male smokers and non-smokers.

Method and materials

This case-control study included 40 male smokers and 40 male non-smokers. Male participants entered the study based on individual biological aspects. Both groups were matched in terms of age, weight, and body mass index. The study was approved by the local ethics committee of Tehran University of Medical Sciences (Ethics code: IR.TUMS.REC.1394.564). Written consent forms were signed by those who volunteered to participate in the study.

Study population

This study is a case-control study that consists of male volunteers who were smokers or non-smokers. Participants were enrolled by the staff of Tehran University of Medical Sciences from August to November 2013. Samples were calculated with a confidence interval of 95% and 90% power of the test. The participants in the control group were matched in terms of age and BMI with the case group. Inclusion criteria were 1. Male, 2. Had the inclination to cooperate; 3. Had at least five cigarettes daily in the past six months in the case group and had no cigarette for at least one year in the control group, 4. Aged between 20 and 55 years. The exclusion criteria were: 1. being female, 2. using another type of tobacco, 3. alcohol usage, 4. suffering from diabetes or cardiovascular diseases, 5. supplementation with any kind of vitamin, mineral, and herbal products, 6. having stomach surgery or suffering from inflammatory bowel diseases, 7. use of anti-acid or H_2 pump blocker medications, 8. being vegetarian, 9. application of Colchicine, Neomycin, Para-aminosalicylic acid and Metformin.

Assessments

Venous blood samples were collected from both groups at the start of the study. The blood samples were examined for the following: fasting glucose, fasting cholesterol, triglyceride, omentin, chemerin, and TNF-α levels. To calculate the daily intake of energy, carbohydrate, protein, fat and some of the micronutrients were used from the 24-h recall and semi-quantitative food frequency questionnaire.

Sample collection

After 10–12 h of fasting, 10 ml of venous blood was drawn from the vein of members of both groups. After separation of the serum, levels of fasting glucose and lipid profiles were quickly determined. The remaining serum sample was kept at $-7\,^{\circ}C$ until the time of use. The serum levels of omentin, chemerin, and TNF-α were determined by enzyme-linked immunosorbent assay (ELISA) using commercial kits.

Statistical analysis

The SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for statistical analyses of data. The nutritionist version 4 software was used to calculate the daily intake of macronutrients and some of the micronutrients from the semi-quantitative food frequency questionnaire. To assess the normal distribution of data, we used the Kolmogorov–Smirnov test and Q–Q plot. To compare the two groups, we used the Student *t*-test and Mann–Whitney test, whenever appropriate. To adjust for possible confounders in our simultaneous comparison, we used the Multivariate Analysis of Covariance (MANCOVA). The relationship of variables was assessed by the Spearman correlation. A *p*-value < 0.05 was accepted as statistically significant.

Results

Demographic, anthropometric, and health characteristics of the participants are presented in Table 1. The table shows that the average age was not statistically different in the case and control group ($p = 0.072$).

The mean $\pm$ standard deviation of daily intake of micro and macronutrients of the participants are presented in Table 2. Table 2 shows that mean daily intake of total fat ($p = 0.002$), saturated fat ($p = 0.021$), and polyunsaturated fatty acid ($p = 0.001$) is statistically different between male smokers and non-smokers.

Also, the daily intake of vitamins E and C in the smoker group was higher than in the non-smoker group, but it was not statistically significant. The mean $\pm$ standard deviation of adipokines in smokers and non-smokers are presented in Table 3. Table 3 shows that there was no significant difference in adipokines levels between smokers and non-smokers ($p > 0.05$). Omentin levels were lower in the smoker group but not statistically significant.

Table 1 Demographic, anthropometric, lipid profile and fasting blood sugar characteristics of the participants.

Variable	Smoker (CI*)	Non-smoker (CI*)	*p*-Value**
Age (year)	36.2 ± 8.5 (32.4–42.8)	41.1 ± 11.3 (35.6–44.7)	0.072
Height (cm)	176 ± 7 (169.8–183.5)	174 ± 16 168.4–182.1)	0.783
Weight (kg)	82.1 ± 11.1 (69.2–88.5)	84.2 ± 11.94 64.4–90.3)	0.81
BMI (kg/m^2)	26.53 ± 3.37 (21.4–29.5)	26.17 ± 3.99 (22.5–28.6)	0.524
TG (mg/dl)	123.2 ± 74.9 (109.6–155.7)	149.2 ± 93.5 (120.3–162.8)	0.08
Cholesterol (mg/dl)	160.5 ± 43.1 (135.7–178.4)	163 ± 41 (138.9–182.4)	0.795
FBS (mg/dl)	81.8 ± 22.7 (68.5–106.4)	82.7 ± 12.6 (71.8–102.7)	0.246

Values are presented as mean ± standard deviation. BMI, body mass index; TG, triglyceride; FBS, fasting blood sugar.
* Confidence interval.
** Based on *t*-test.

Table 2 Daily intake micro and macronutrient of the participants.

Variable	Smoker (CI*) [*n* = 40]	Non-smoker (CI*) [*n* = 40]	*p*-Value**
Energy (kcal)	2316.66 ± 59.11 (1843.68–2568.91)	2088.9 ± 76.02 (1784.71–2265.44)	0.40
Carbohydrate (g)	376.88 ± 14.29 (286.87–401.82)	346.14 ± 11.48 (262.76–421.55)	0.09
Protein (g)	84.41 ± 2.16 (68.34–98.46)	80.72 ± 2.08 (71.54–96.36)	0.22
Fat (g)	95.92 ± 29.84 (58.64–104.22)	58.35 ± 2.95 (45.22–78.66)	0.002
Saturated fatty acid	15.27 ± 6.46 (9.34–21.65)	12.42 ± 4.54 (7.23–18.78)	0.021
Poly unsaturated fatty acid (g)	6.62 ± 4.75 (4.54–9.21)	3.66 ± 2.29 (2.49–6.65)	0.001
Selenium (μg)	0.04 ± 0.024 (0.01–0.07)	0.041 ± 0.026 (0.02–0.09)	0.927
Vitamin E (mg)	3.92 ± 1.25 (2.83–6.75)	3.5 ± 1 (3.1–8.43)	0.107
Vitamin C (mg)	184.05 ± 85.19 (105.66–200.76)	174.22 ± 80.87 (123.76–208.65)	0.603

Values are presented as mean ± standard deviation.
* Confidence interval.
** Based on *t*-test or Mann–Whitney test, whenever appropriate.

Table 3 Serum levels of adipokines of the participant by smoking status.

Variable	Smoker (CI*)	Non-smoker (CI*)	*p*-Value**
TNF-α (pg/mL)	205.4 ± 121.11 (186.63–319.81)	326.87 ± 306.52 (196.71–342.92)	0.961
Omentin (ng/m/L)	117.03 ± 27.87 (101.52–187.86)	255.85 ± 335.33 (142.65–292.96)	0.578
Chemerin (μg/l)	650.72 ± 756.01 (540.43–823.12)	840.95 ± 1086.36 (619.23–895.28)	0.566

Values are presented as mean ± standard deviation. TNF-α, tumour necrosis factor-alpha.
* Confidence interval.
** Based on Mann–Whitney test.

Table 4 The relationship of adipokines with smoking duration and smoking number.

Variable	Smoking number (*n* = 40)		Duration of smoking (*n* = 40)	
	r	*p*	*r*	*p*
TNF-α	−0.273	0.016	−0.282	0.013
Omentin	−0.260	0.021	−0.262	0.021
Chemerin	−0.146	0.205	−0.078	0.0503

r: Spearman correlation coefficient.

Correlation between smoking duration and number of cigarettes smoked with TNF-α, omentin and chemerin is presented in Table 4 and Fig. 1. Table 4 shows that an increase in the number of cigarettes smoked and smoking duration decreases the serum levels of TNF-α, omentin and chemerin. Correlation between TNF-α, and omentin with smoking duration and number of cigarettes smoked is statistically significant, but the correlation with chemerin is not statistically significant.

Comparison of serum levels of adipokines after adjustment for age, total fat, and saturated fatty acid intakes by multivariate analysis of covariance is presented in Table 5

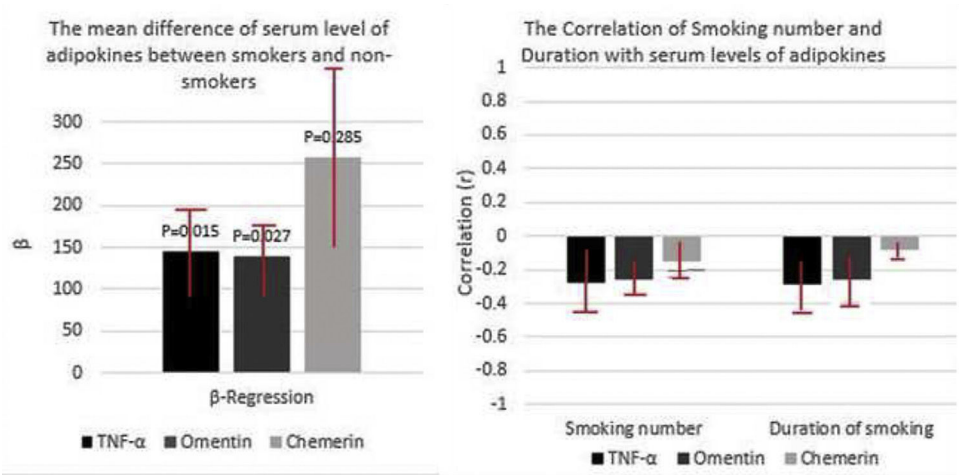

Figure 1 Comparison of adipokines serum levels between two groups and its correlation with smoking number and duration.

Table 5 The mean differences of serum level of adipokines between smokers and non-smokers after adjusting confounder effects.

Dependent variable	β	95% confidence interval	p-Value*
TNF-α	144.5	(28.9–260.2)	0.015
Omentin	138.4	(16.2–260.6)	0.027
Chemerin	257.2	(−218.4–732.7)	0.285

β: Regression coefficient.
* Based on Multivariate analysis of Covariance (MANCOVA).

and Fig. 1. It shows that when the two groups were adjusted in terms of total fat and saturated fat intake, the difference of omentin ($p = 0.027$) and TNF-α ($p = 0.015$) in the two groups was statistically significant, but serum levels of chemerin were not statistically significant.

Discussion

In the present study, we compared the serum levels of omentin, chemerin, and TNF-α and some of the micronutrient intakes in male smokers and non-smokers. Our study showed that omentin, chemerin, and TNF-α levels in male smokers were lower than in non-smokers. However, the difference was not statistically significant. But after adjustment for total fat and saturated fatty acid intake, omentin and TNF-α levels in the two groups were statistically significant and also mean daily intake of vitamins E and C in smokers were higher than non-smokers, probably because the total caloric intake is higher in smokers, although these differences are not statistically significant. Daily intake of selenium did not differ significantly between smokers and non-smokers. To the best of our knowledge, this is the first study that compared the serum levels of omentin, chemerin, and TNF-α in male smokers and non-smokers.

Serum adipokine concentrations are lower in women than women. The sexual dimorphism for adipokine has been attributed to the direct effects of testosterone on adipose tissue adipokine secretion.[20] However, in addition to sex and testosterone levels, other factors such as smoking and oxidative stress affect the levels of adipokines such as omentin, chemerin, and TNF-α.

Hypoxia leads to oxidative stress in adipocytes and alters the secretion of adipokines.[21] Adaptive response of the body to changes in oxygen tension (hypoxia) is the production of HIF-1 which is a transcription factor that binds to the hypoxia response element and activates hypoxia gene transcription. The result of these changes in gene expression is a decreased secretion of adipocytokines such as adiponectin and an increased level of TNF-α.[21] Xu et al. observed that the HIF-1α level of the smoking group was higher than asthma and control groups and cigarette smoking activates HIF-1α.[22] Maternal cigarette smoking may be associated with villus hypoxia and the gene expression level of HIF1A in the active smoker group was significantly higher than that in the non-smoker group.[23] FU et al. reported that chronic intermittent hypoxia leads to insulin resistance via dysregulation of adiponectin and leptin in non-obese rodents.[24] There are numerous studies on the relationship between adiponectin and chemerin and omentin, and smoking also provokes oxidative stress and inflammatory cytokines such as TNF-α. Also, smoking inhibits the expression of the adiponectin gene. There is a significant relationship between adiponectin and TNF-α expression in adipose tissue. It is demonstrated that in persons with high plasma adiponectin levels, the level of TNF mRNA expression is lower.[25,26] Our results show that serum levels of TNF-α, omentin, and chemerin in the smoker group are lower than the non-smoker group. However, the difference between the two groups was not statistically significant. On the other

hand, smoking causes oxidative stress and decreased serum levels of vitamins E and C in the body. For this reason, it is suggested that a greater amount of vitamins E and C should be consumed by smokers to reduce the negative effects of smoking.[27] Vitamin C is a cofactor in the hydroxylation reaction and also plays a role in the biosynthesis of collagen.[28] Selenium as an antioxidant can reduce the expression of pro-inflammatory genes, including TNF-α and cyclooxygenase 2.[29] The Landrier et al. study showed adiponectin expression is induced by vitamin E via a PPAR-γ dependent mechanism and the difference between the two groups was statistically significant. Vitamin E resulted in an induction of adiponectin at mRNA and protein levels.[29] Vincent et al. found that in the group that received antioxidant supplements, adiponectin levels were increased after 6 weeks.[16] In another study, it was reported that vitamin C supplementation did not influence adiponectin concentration.[28] Maybe one of the reasons for the lower serum levels of chemerin and TNF-α in smoker group may be due to higher intakes of polyunsaturated fatty acid in this group, because increased intake of fatty acids can affect the expression of inflammatory factors such as TNF-α.[30]

Conclusion

The serum levels of omentin, chemerin, TNF-α, and nutrients intakes including energy, protein, carbohydrate, fat, vitamin E, C and selenium were not significantly different between smokers and non-smokers. But after adjustment of age, total fat and saturated fatty acid intakes, the mean difference of omentin and TNF-α was significant between the two groups. But for more precise conclusions, further population-based studies are needed to clarify the serum level of these adipokines in male smokers.

Limitations

There are some notable limitations in our study. First of all, stratification of the smoking group was done on the basis of self-reported smoking habits, and the second limitation was the lack of precise measurement of visceral and subcutaneous fat mass compartments, which are known to be more strongly related to adipokine levels. Also, considering the effect of sex on the level of adipokines, it is suggested that in future studies, the effect of smoking on adipokines in women be investigated.

Authors' contributions

SF, MM, and NP drafted the article. MHJ and MDj. NP, and NMH made a substantial contribution to the concept or design of the work. MM, NS, and MA made a substantial contribution to the acquisition of data. MY and SF made a substantial contribution to the data analysis. NP, MM, MZ, and NMH revised the manuscript critically. All authors approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.REC.1394.564) and conducted according to the Helsinki declaration. All subjects provided written informed consents.

Consent to publication

Written informed consent was obtained from the participants for the publication of the results of this research.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding authors on reasonable request.

Funding

Not applicable.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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