Plasma Leptin Concentrations After Cessation Of Cigarette Smoking

Sigara Bırakmanın Plazma Leptin Düzeylerine Etkisi

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Özet

Sigara bırakılması hiperfaji ve enerji tüketiminde azalma ile ilişkili olarak genellikle kilo artışına yol açmaktadır. Plazma leptin ve doku mRNA düzeyleri yağ dokusu kütlesi ile korelasyon gösterir ve vücut toplam enerji düzeyinin habercisi olarak kabul edilir. Bu çalışmada sigara bırakma kliniğine başvuran 19 tiryaki (13 E/6 K) rastgele, kontrol grubu (n:6), nikotin bandı (n:6) ve nikotin bandı+fluoksetin (n:7) tedavi grupları olarak sınıflandırıldı. Plazma leptin düzeyleri ve vücut kitle indeksi (VKİ) sigara bırakılmasından önce, bırakılmasından 3 ve 6 hafta sonra değerlendirildi. Başlangıç değerlerine göre 3. ve 6. haftalarda leptin düzeyleri (p 0.02) ve VKİ'de (p 0.01) anlamlı bir artış saptandı. Başlangıç ve 3. hafta VKİ arasındaki farka etkili değişkenlerin %66.6'sını açıklayan (p:0.007) genel düzlemsel analize göre nikotin bandı+ fluoksetin tedavisi, leptin düzeyleri ve ekshale edilen CO düzeyleri etkili faktörler olarak saptandı. Başlangıç ve 3. hafta leptin düzeylerindeki değişkenliğin %55.4'ünü (p: 0.027) açıklayan modele göre plazma leptin düzeyleri artışı vücut ağırlığı artışı ve nikotin bandı+fluoksetin tedavisi ile ilişkili bulunmuştur. Sigara bırakılmasını takiben plazma leptin konsantrasyonları artmıştır. Fluoksetin kilo artışını engellerken, leptin düzeylerini artırıcı yönde etki göstermiştir. Sonuçlarımız Fluoksetinin leptin düzeylerine etkisinin kilo değişiminden bağımsız olduğu düşündürmektedir.

Anahtar Kelimeler: Leptin, Sigara bırakılması, Vücut kitle indeksi, Nikotin bandı, Fluoksetin.

Abstract

Cessation of smoking often induces hyperphagia and weight gain associated with decreased energy expenditure. Plasma leptin levels and adipose tissue mRNA correlate with mass of adipose tissue, and represent important signals for registration of total body energy status. In this study 19 smokers (13 male, 6 female) referring to the smoking cessation clinic were randomly assigned to control group (n:6), nicotine patch group (n:6), nicotine patch+fluoxetine group (n:7). Plasma leptin levels and, body mass indices (BMI) were determined before and 3, 6 weeks after cessation of smoking. A significant increase in BMI (p: 0.01) and in plasma leptin (p: 0.02) were observed in the 3rd and 6th weeks compared to basal levels. The univariate analysis of variance which explained 66.6% variance (p: 0.007) in body weight between 0 and 3 weeks, has indicated nicotine patch+ fluoxetine therapy, the difference in leptin levels, and difference in exhaled carbon monoxide levels as the significant contributors. The difference in body weight, study groups, and age at time of starting smoking were the significant contributors to 55.4% variance (p: 0.027) in leptin levels between 0 and 3 weeks. Plasma leptin increased together with body weight and nicotine patch+fluoxetine theraphy vs. controls. Plasma leptin concentrations have increased after cessation of cigarette smoking in vivo. Fluoxetine has an enhancing effect on leptin alongside inhibiting weight gain. We conclude that fluoxetine treatment might independently increase leptin levels.

Key Words: Leptin, Cessation of smoking, Body mass index, Nicotine patch, Fluoxetine.

Introduction

Despite knowledge of health risks, only 2.5% of smokers each year achieve abstinence. Although much of the inability to quit smoking can be attributed to the addictive nature of ingredients, studies have shown subsequent weight gain as an important deterrent to quitting smoking (1,2). Williamson et al. estimated that the mean weight gain attributable to cessation of cigarette smoking was 2.8 kg in men and 3.8 kg in women examined in NHANES I and the Follow-Up Study. In NHANES II a negative relationship between cigarette smoking and body weight has been demonstrated (3-5). Leptin is a hormone secreted mainly by the adipocytes and has a role in metabolic adaptation, acting in the regulation of bodyweight (6). A number of cross-sectional studies have shown lower leptin levels in chronic smokers suggesting leptin as a candidate mechanism that contributes to the inverse relationship between smoking and body weight (5,7,8). However cross-sectional studies can be biased by subject characteristics such as gender, age, and ethnicity and other lifestyle behaviors, confounded with smoking status (5,7,8). In this prospective, self-controlled study we aimed to determine leptin changes following cessation of smoking independently from patients' personal characteristics.

MATERIAL AND METHODS

Study Group

The study was conducted at Gaziantep University, Faculty of Medicine Department of Pulmonary Diseases, and Department of Biochemistry and Clinical Biochemistry in 2004. Informed consent was obtained from all subjects according to the Helsinki declaration as revised in 1996. Nineteen smokers (13 male, 6 female mean± SD age: 43.8±11.2, min-max: 24-68 years) referring to the smoking cessation clinic were randomly assigned to control group (n: 6), nicotine patch group (n: 6), nicotine patch+ fluoxetine group (n: 7).

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Ages of the participants at the time of starting smoking were (mean± SD: 18.4 ±6.0, min-max: 8-38 years), average number of cigarettes they smoked per day were (mean± SD: 29.5 ±15.2, min-max: 10-80), and duration of smoking were (mean± SD: 24.3 ±9.3, min-max: 10-42 years).Nicotine replacement therapy with nicotine patches containing 52.5mg nicotine (Nicotinell TTS 30 cm^2, Novartis), 35mg nicotine (Nicotinell TTS 20 cm^2, Novartis) and 17.5mg nicotine (Nicotinell TTS 10 cm^2, Novartis) were provided two weeks each sequentially. Fluoxetine 20mg/day was started 3 weeks before the target quit day and was continued for 3 months thereafter. Plasma leptin levels, exhaled carbon monoxide levels and, body mass index (BMI) were determined before and 3, 6 weeks after cessation of smoking. Subjects receiving any systemic or topical therapy within at last month preceding the study or having an established diagnosis of any systemic disease with either clinical or laboratory signs were excluded.

Clinical Study

Blood samples were collected using standard venipuncture technique between 9:30 to 11:00 am after 10-12 h fast. Serum samples were separated immediately after centrifugation at 4°C, 2000 g for 10 min and stored at–20°C until analysis, which were performed in the same run to avoid inter-run analytical variation. Serum leptin levels were measured with Sandwich ELISA, with HRP-labeled antibody according to the manufacturer's instructions (Human Leptin ELISA, BioSource International, California, USA). The lower detection limit of the assay was 0.5 ng/mL, intra-assay and inter-assay coefficients of variation were between 3.0-3.8% and 3.9-4.7% respectively.

Statistical Analyze

Data are presented as mean ± SEM or median (min–max). Comparison of variables was performed with the Mann Whitney U test. Significant influences on variation of leptin levels were evaluated with general linear model.

Two-tailed $p<0.05$ was considered significant. Analyses and illustrations were performed with SPSS 9.0 (SPSS Inc., Chicago, IL, USA) statistical software program.

Results

A significant increase in BMI (p: 0.01) and in plasma leptin (p: 0.02) were observed in the 3rd and 6th weeks compared to basal levels, whereas 3rd and 6th week leptin concentrations and BMI were comparable (p0.05) (Table 1).

The univariate analysis of variance which explained 66.6% variance (p: 0.007) in body weight between 0 and 3 weeks, has indicated nicotine patch+ fluoxetine therapy, the difference in leptin levels, and difference in exhaled carbon monoxide levels as the significant contributors, controlling for gender, the difference in leptin concentration, the difference in exhaled carbon monoxide levels, depression score, age at time of starting smoking, and study groups (Table 2).

Table 1. Weight, BMI, exhaled CO and plasma leptin levels before and 3, 6 weeks after cessation of smoking (median: 25th -75th percentiles).

	Basal	3rd week	6th week	p
CO (ppm)	20.0: 11.0-22.0	2.0: 1.0-4.0	2.0: 1.0-2.0	0.000 * 0.001 **
Weight (kg)	70: 60-75	72: 62-78	74: 66-81	0.001 * 0.007 **
BMI kg/m2	24.4:23.3-27.5	24.9: 23.9-28.7	24.2: 26.3-28.6	0.001 * 0.007 **
Leptin ng/mL	2.59: 1.60-5.41	3.19: 2.40- 7.05	3.52: 2.32-9.24	0.011 * 0.008 **

basal vs.3rd rd week
basal vs. 6th week

Table 2. Univariate analysis of variance of; difference in leptin levels, and difference in BMI, before and 3 weeks after cessation of smoking as the dependent variables.

	Variance in leptin (ng/mL)			Variance in body weight (kg)		
	p	B	SE	p	B	SE
Corrected model	0.026			0.007		
Intercept	0.015			0.056		
Difference in exhaled CO (ppm)	0.059	0.15	0.07	0.014	-0.13	0.04
Depression score	0.246	-0.06	0.05	0.292	0.04	0.04
First smoking age (years)	0.030	-0.21	0.08	0.067	0.13	0.06
Difference in weight (kg)	0.001	1.17	0.26	-	-	-
Difference in leptin (ng/mL)	-	-	-	0.001	0.58	0.13
Nicotine patch vs. control	0.269	1.61	1.38	0.346	-0.98	0.99
Nicotine patch+fluxetine vs. control	0.044	4.02	1.75	0.043	-2.85	1.23
Gender (M vs. F)	0.412	-0.33	1.55	0.955	0.061	1.09
Adjusted R^2	0.554			0.666		

Body weight increased by 0.58±0.13 kg/m2 for each unit increase of leptin (ng/mL) (p: 0.001), decreased 2.85±1.23kg/m2 for nicotine patch+ fluoxetine therapy vs. controls (p: 0.043), and decreased 0.13±0.04 kg/m2 for each unit decrease in exhaled carbon monoxide levels (p: 0.014).

The univariate analysis of variance which explained 55.4% variance (p: 0.027) in leptin levels between 0 and 3 weeks, has indicated the difference in body weight, study groups, and age at time of starting smoking as the significant contributors, controlling for gender, difference in body weight, difference in exhaled carbon monoxide levels, depression score, age at time of starting smoking, and study groups (Table 2). Plasma leptin increased by 1.17±0.26 ng/mL for each unit increase in body weight (kg) (p: 0.001), increased 4.02±1.75 ng/mL for nicotine patch+fluoxetine theraphy vs. controls (p: 0.044) and decreased 0.21±0.08 ng/mL for each year of age at starting smoking (p: 0.30).

Discussion

The first finding of this study is an increase in body weight and leptin levels after quitting smoking, as expected (5,7). It can also be suggested that the major change in body weight and leptin levels takes place within the first weeks as there is no significant difference between 3rd and 6th weeks. The second important data is about the factors that contribute to the variation in leptin levels and BMI following cessation of smoking. Increased levels of leptin are likely a reflection of increased fat deposition, since leptin provides information about the size of the fat stores, establishing a communication between the energy reserves and the hypothalamic centers that control food intake (1,5,8,10).

However it is difficult to say that, smokers have lower leptin levels just because they are leaner, because our models explain half of the variations. Fluoxetine, a selective serotonin reuptake inhibitor is commonly used as an antidepressant and has also been suggested as an adjunct to other strategies to treat obese individuals (6). Nicotine patch+ fluoxetine therapy was associated with a significant reduction in variation of body weight and a significant increase in variation of leptin levels compared to the controls.

This result can be partly explained with fluoxetine's side effect about body weight, and is consistent with the concept that, nicotine may independently reduce weight gain via i.e. decreased appetite and fat deposition, and increased energy expenditure (5,6,10). However the discrepancy between effects of fluoxetine on body weight and leptin levels was surprising. Taking into account that increased leptin levels inhibits appetite; these results could represent a direct stimulatory effect of fluoxetine on leptin levels that leads to reduced weight gain (compared to controls) rather than increased leptin resistance. It is established that serotonergic system has enhancing effect on leptin (9).

Previously Esel at al. reported increased leptin levels in response to antidepressants in patients with major depression (10). Serotonergic neurons present leptin receptor immunoreactivity and mRNA, indicating the possibility of a direct action of leptin on this neurotransmitter system. Acute and chronic treatment with fluoxetine causes a decrease in leptin levels in rat models; however, the effect of chronic fluoxetine administration on leptin levels in human subjects deserves further investigation (6).

We conclude that fluoxetine treatment might independently increase leptin levels. We did not observe a difference for gender in variation of neither leptin levels nor body weight responses to cessation of smoking. Previously Esel at al. reported similar results. Difference in exhaled carbon monoxide levels rather than smoked cigarettes per day was a significant contributor to variation in BMI possibly representing degree of addiction. This can be due to presence of lib smokers, who smoke more cigarettes per day but have lower carbon monoxide levels.

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