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Smoking Habits and Neuropeptides: Adiponectin, Brain-derived Neurotrophic Factor, and Leptin Levels

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This study aimed to identify changes in the level of neuropeptides among current smokers, former smokers, and individuals who had never smoked, and how smoking habits affect obesity and metabolic syndrome (MetS). Neuropeptide levels, anthropometric parameters, and metabolic syndrome diagnostic indices were determined among male workers; 117 of these had never smoked, whereas 58 and 198 were former and current smokers, respectively. The total sample comprised 373 male workers. The results obtained from anthropometric measurements showed that current smokers attained significantly lower body weight, body mass index, waist circumference, and abdominal fat thickness values than former smokers and those who had never smoked. Current smokers' eating habits proved worse than those of non-smokers and individuals who had never smoked. The level of brain-derived neurotrophic factor (BDNF) in the neuropeptides in the case of former smokers was 23.6 ± 9.2 pg/ml, higher than that of current smokers (20.4 ± 6.1) and individuals who had never smoked (22.4 ± 5.8) ($F = 6.520$, $p = 0.002$). The level of adiponectin among former smokers was somewhat lower than that of current smokers, whereas leptin levels were higher among former smokers than current smokers; these results were not statistically significant. A relationship was found between adiponectin and triglyceride among non-smokers (odds ratio = 0.660, β value = –0.416, $p < 0.01$) and smokers (odds ratio = 0.827, β value = –0.190, $p < 0.05$). Further, waist circumference among non-smokers (odds ratio = 1.622, β value = 0.483, $p < 0.001$) and smokers (odds ratio = 1.895, β value = 0.639, $p < 0.001$) was associated with leptin. It was concluded that cigarette smoking leads to an imbalance of energy expenditure and appetite by changing the concentration of neuropeptides such as adiponectin, BDNF, leptin, and hsCRP, and influences food intake, body weight, the body mass index, blood pressure, and abdominal fat, which are risk factors for MetS and cardiovascular disease.

Key words: Smoking habits, Neuropeptides, Adiponectine, BDNF, Leptin

INTRODUCTION

Smoking and obesity have been identified as a major risk factor for premature death in some developed countries and those experiencing rapid economic growth (1,2). The two can be attributed to poor lifestyle habits and are closely associated with chronic metabolic diseases such as preventable diabetes, hypertension, metabolic syndrome (MetS), and cardiovascular disease (CVD) (3,4).

Although smoking and obesity independently cause the above-mentioned diseases, there is a relationship between the two. The fact that individuals who quit smoking gain weight after quitting indicates a relationship between smoking and obesity (or being overweight) (5,6). The correlation between these can be confirmed by proving the biological mechanism involved in the interaction between smoking and neuropeptides such as adiponectin (AdipoN), brain-derived neurotrophic factor (BDNF), and leptin (LeP); these are associated with energy balance in the body. Neuropeptides are a peptide hormone associated with food intake and energy expenditure, which, in turn, regulate the body's energy balance (7,8). LeP binds to the LeP receptor in the hypothalamus, subsequently producing JK2 (janus kinase 2)-STAT3 (a signal transducer and activator of transcription 3) and phosphatidylinositol-3 kinase (PI3K), activating the sympathetic, and increasing the metabolic ratio. Thus, LeP reduces food intake and body weight (9). AdipoN is one of the neuropeptides secreted by fat cells, which binds to the AdipoN 1 receptor located in the brain's endothelial cells

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and the hypothalamus (controls insulin sensitivity). In addition, it has been known to be involved in the regulation of obesity (controls energy expenditure) by binding to the AdipoN 2 receptor (10). Though AdipoN and LeP cause obesity and diabetes, the action is opposite (11,12).

Obese adults have been reported to have a higher level of LeP, but a lower level of AdipoN, as compared to non-obese adults (13). According to Davies (14) and McAllister (15), BDNF is known for its important role in the survival, proliferation, and differentiation of neurons in the central and peripheral nervous systems, as well as regulating food intake and body weight by binding to the tropomyosine-related kinase (Trk) family receptor (7). In previous studies, weight loss among smokers has been associated with certain neurotransmitters (16) and occurs as a result of lower food intake and higher energy expenditure (17). The absorption of nicotine through smoking increases the production of neurotransmitters such as dopamine and serotonin, and inhibits the expression of LeP. This results in lower dietary intake (18). Moreover, nicotine inhibits the expression of the mRNA of BDNF and AdipoN, and reduces the body's energy expenditure. However, non-absorption of nicotine would lead to an increase in AdipoN and BDNF (19,20).

The objective of this study is to identify any changes in the level of neuropeptides among current smokers, former smokers, and individuals who have never smoked. In addition, the study aims to determine the effect of smoking habits on obesity and MetS. The study sample consisted of male workers.

MATERIAL AND METHODS

Study subjects. The study subjects were 373 male workers; among these, 198 were current smokers, 58 were former smokers, and 117 had never smoked before. These workers had not been exposed to chemicals that can have an effect on neuropeptides. The study was approved by the Institutional Review Board of the Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency. The authors visited the selected workplace and carefully explained the study's objectives, procedures and methods, as well as the privacy policy and other related matters to the workers. Each participant provided informed consent to participate in the study.

MetS diagnostic indices and the measurement of anthropometric parameters. MetS was identified by the presence of three or more of the five components listed below in the NCEP-ATP III diagnostic criteria (Asia-Pacific) (21): i) Abdominal obesity: waist circumference ≥ 102 cm for men; ii) Triglycerides: 150 mg/dl; iii) High-density lipoprotein cholesterol: < 40 mg/dl for men; iv) Blood pressure: systolic/diastolic ≥ 130/85 mmHg; and v) Fasting glucose: > 110 mg/dl. Weight, height, and the BMI were measured with a body composition analyzer (X-SCAN plus II, Jawon Medical, Seoul, Korea). Systolic and diastolic blood pressure was measured with the mercury manometer after a 10-minute rest. Subcutaneous fat thickness (SFT) and visceral fat thickness (VFT) were measured with ultrasonic diagnostic equipment (SonoAce 8800, Medison Co., Seoul, Korea), using a B mode ultrasound 3.5 MHz oval probe.

Serum biochemistry test. Blood was collected from 09:00 AM to 10:00 AM from workers who had been in a fasting state since 10:00 PM the previous day. Separated serum was transported to the laboratory in frozen form. Serum biochemistry tests for fasting glucose, triglyceride, total cholesterol, and HDL-cholesterol and LDL-cholesterol were conducted with an automatic biochemistry analyzer (COBAS integra 400, Roche Diagnostics Ltd., Rotkreuz, Switzerland). Cortisol and serum insulin were measured with an automatic chemiluminescence immune analyzer (Sanofi Diagnostics Pasteur, Inc., Minnesota, USA), and homeostasis model assessment of insulin resistance was calculated through the equation, [HOMA-IR = fasting insulin (μIU/ml) × fasting glucose (mg/dl)/405].

Measurement of neuropeptides. The sandwich ELISA kit (LINCO Research Inc., Missouri, USA) was used to measure LeP in serum. In addition, AdipoN and BDNF were measured with the sandwich ELISA kit (R&D systems, Minnesota, USA), using the method proposed by the manufacturer. The absorbance of high sensitivity C-reactive protein concentration (hsCRP) was measured at 660 nm by the Micro-protein analysis system LX-2200 (Aloka, Tokyo, Japan) in proportion to the hsCRP concentration of the condensed sample following the reaction of latex particles coated with anti-hsCRP and serum.

RESULTS

Total subject and group characteristics. The subjects' mean age was 39.3 years. Current smokers' mean age was 38.1 years, which was significantly lower than that of former smokers (41.9 years) and the group that had never smoked (40.1 years) ($F = 4.380$, $p = 0.013$). Anthropometry measurement results showed that current smokers have a significantly lower body weight and BMI, waist circumference, and abdominal fat thickness values than former smokers and the group that had never smoked. In addition, the difference between current smokers and former smokers, in this regard, was found to be significantly larger than that between current smokers and the group that had never smoked before (Table 1). Current smokers' eating habits were shown to be worse than those of individuals who had never smoked and former smokers. Measurement results for clinical bio-

Table 1. Total subject and group characteristics

	Total (n = 373)	Current smokers (n = 198)	Ex-smokers (n = 58)	Never smokers (n = 117)	Statistics, p-value
Age, years	39.3 ± 9.1	38.1 ± 8.5	41.9 ± 8.1	40.1 ± 10.1	F = 4.380, p = 0.013
Anthropometric parameters					
Body weight, kg	68.3 ± 10.1	67.8 ± 10.1	71.3 ± 11.2	67.7 ± 9.5	F = 3.025, p = 0.050
Body mass index, kg/m^2	23.3 ± 2.9	23.0 ± 3.1	24.0 ± 2.8	23.5 ± 2.5	F = 2.932, p = 0.055
Waist circumference, cm	83.1 ± 8.0	82.1 ± 8.2	85.9 ± 7.8	83.3 ± 7.6	F = 5.278, p = 0.005
Subcutaneous fat thickness, cm	1.57 ± 0.55	1.47 ± 0.54	1.66 ± 0.46	1.70 ± 0.58	F = 7.385, p = 0.001
Visceral fat thickness, cm	4.12 ± 1.40	3.99 ± 1.38	4.60 ± 1.35	4.09 ± 1.41	F = 4.267, p = 0.015
Systolic BP, mmHg	127.4 ± 14.5	126.9 ± 14.4	126.7 ± 11.8	128.4 ± 15.8	F = 0.451, p = 0.637
Diastolic BP, mmHg	75.3 ± 10.2	74.7 ± 10.2	75.7 ± 8.5	75.9 ± 11.2	F = 0.551, p = 0.577
Food intake score	20.7 ± 2.9	20.4 ± 2.8	20.9 ± 2.6	21.1 ± 3.0	F = 2.303, p = 0.049
Clinical parameters					
Fasting glucose, mg/dl	92.1 ± 19.1	91.7 ± 16.5	97.1 ± 32.2	90.0 ± 12.3	F = 2.642, p = 0.073
Triglyceride, mg/dl	179.4 ± 145.1	190.8 ± 158.5	163.1 ± 107.4	166.2 ± 134.9	F = 1.365, p = 0.257
Total Cholesterol, mg/dl	189.4 ± 33.9	187.7 ± 32.8	191.7 ± 34.5	191.5 ± 35.7	F = 0.551, p = 0.577
HDL-Cholesterol, mg/dl	49.9 ± 11.5	50.0 ± 11.1	51.0 ± 13.3	48.9 ± 11.1	F = 0.638, p = 0.529
LDL-Cholesterol, mg/dl	111.0 ± 30.5	107.1 ± 30.1	115.5 ± 25.1	116.2 ± 33.2	F = 3.628, p = 0.028
Insulin, μIU/ml	7.64 ± 6.98	7.77 ± 7.94	7.61 ± 5.65	7.40 ± 5.53	F = 0.096, p = 0.908
HOMA-IR	3.25 ± 3.36	3.30 ± 3.83	3.35 ± 2.73	3.07 ± 2.61	F = 0.184, p = 0.832

BP, blood pressure; HOMA-IR, homeostasis model assessment-insulin resistance.

Table 2. Hormonal measures

	Total (n = 373)	Current smokers (n = 198)	Ex-smokers (n = 58)	Never smokers (n = 117)	Statistics, *p*-value
Cortisol, nmol/l	290.3 ± 92.8	283.1 ± 91.8	297.1 ± 94.3	300.5 ± 93.6	F = 1.348, p = 0.261
C-reactive protein, mg/dl	0.21 ± 0.23	0.19 ± 0.22	0.24 ± 0.28	0.21 ± 0.22	F = 1.079, p = 0.341
Adiponectin, ng/ml	3.51 ± 3.18	3.67 ± 3.01	3.04 ± 2.58	3.44 ± 3.76	F = 0.838, p = 0.434
BDNF, pg/ml	21.3 ± 7.4	20.9 ± 6.8	23.6 ± 9.2	20.6 ± 7.0	F = 3.613, p = 0.028
Leptin, ng/ml	4.40 ± 3.09	4.12 ± 3.04	4.68 ± 2.59	4.72 ± 3.43	F = 1.246, p = 0.289

BDNF, brain-derived neurotrophic factor.

chemistry parameters showed that LDL-cholesterol concentration levels were at 107.1 ± 30.1 mg/dl for current smokers, 115.5 ± 25.1 mg/dl for former smokers, and 116.2 ± 33.2 mg/dl for individuals who had never smoked. LDL-cholesterol concentration levels were significantly low among current smokers (F = 3.628, p = 0.028). No significant difference was found in the levels of fasting glucose among all groups; however, fasting glucose levels were higher among former smokers (97.1 ± 32.2 mg/dl) than current smokers and those who had never smoked (F = 2.642, p = 0.073). No significant differences according to smoking habits were found with regard to the values obtained for triglyceride, total cholesterol, HDL-cholesterol, insulin, and HOMA-IR.

Levels of neuropeptides according to smoking status. Table 2 presents neuropeptides, hormones, and cytokine concentrations according to smoking habits. The level of BDNF in the neuropeptides in the case of former smokers was 23.6 ± 9.2 pg/ml, which was relatively higher than that of current smokers (20.9 ± 6.8 pg/ml) and those who had never smoked (20.6 ± 5.8 pg/ml) (F = 3.613, p = 0.028). The level of AdipoN among former smokers was somewhat lower than that of current smokers. In contrast, the level of LeP among former smokers was higher than that of current smokers. However, both sets of results were not statistically significant.

Correlation between neuropeptides, obesity, and smoking habits. Table 3 presents the results obtained from the correlation analysis, referring to the number of cigarettes smoked per day, duration of smoking, eating hab-

Table 3. Pearson's correlation coefficients of neuropeptides with smokers

Parameters	Correlation coefficient	
	Cigarettes per day	Smoking period
Food intake	−0.100	−0.237*
Adiponectin	−0.181	0.029
BDNF	0.044	0.251
Leptin	0.226*	−0.066

*$p < 0.05$. BDNF, brain-derived neurotrophic factor.

Table 4. Comparisons of neuropeptides levels in non-obese and obese by smoking habit

Neuropeptides	Groups (n = 373)					t-test*
	Total (n = 373)	Never smokers (n = 106)	Ex-smokers (n = 66)	Current smokers (n = 201)	Statistics, p value	p value
Non-obese (BMI < 25 kg/m^2)	(n = 256)	(n = 69)	(n = 35)	(n = 152)		
AdipoN	3.8 ± 3.2	3.7 ± 3.9	3.9 ± 2.6	3.8 ± 3.0	F = 0.029, 0.971	0.002
BDNF	20.9 ± 6.9	20.5 ± 6.5	22.9 ± 8.5	20.6 ± 6.6	F = 1.855, 0.159	0.042
Leptin	3.3 ± 1.9	3.5 ± 2.0	3.4 ± 1.8	3.2 ± 1.8	F = 0.400, 0.671	0.000
Obese (BMI ≥ 25 kg/m^2)	(n = 117)	(n = 37)	(n = 31)	(n = 49)		
AdipoN	2.5 ± 2.8	2.6 ± 3.5	1.6 ± 2.0	3.0 ± 2.6	F = 1.457, 0.239	
BDNF	22.7 ± 8.6	20.8 ± 8.6	25.6 ± 9.9	22.5 ± 7.7	F = 1.917, 0.153	
Leptin	6.9 ± 3.8	7.4 ± 4.6	6.2 ± 2.5	6.9 ± 3.8	F = 0.589, 0.558	

*Significantly different between total level of non-obese and obese (by t-test); AdipoN, adiponectin; BDNF, brain-derived neurotrophic factor.

Table 5. Interrelationship adjusted age, gender, food intake, drinking and exercise habit between life habit and neuropeptides with components of metabolic syndrome using multiple logistic regression analysis

Independent variables	Dependent variables (n = 315)					
	Waist C. Odds (β value)	Blood pressure Odds (β value)	HDL-Cholesterol Odds (β value)	Triglyceride Odds (β value)	Fasting glucose Odds (β value)	MetS Odds (β value)
Adiponectin						
NS (n = 117)	0.823 (–0.195)	0.849 (–0.164)	0.793 (–0.232)	0.660 (–0.416)**	2.122 (9.963)	0.776 (–0.253)
CS (n = 198)	0.879 (–0.128)	0.973 (–0.027)	0.844 (–0.170)†	0.827 (–0.190)*	0.848 (–0.165)	0.861 (–0.150)
BDNF						
NS (n = 117)	0.936 (–0.066)	0.976 (–0.024)	0.981 (–0.019)	0.960 (–0.041)	4.469 (6.102)	0.968 (–0.033)
CS (n = 198)	0.960 (–0.041)	1.046 (0.045)†	0.989 (–0.011)	0.984 (–0.016)	0.971 (–0.030)	0.988 (–0.012)
Leptin						
NS (n = 117)	1.622 (0.483)***	1.037 (0.036)	0.920 (–0.084)	0.998 (–0.002)	4.305 (15.275)	0.945 (–0.057)
CS (n = 198)	1.895 (0.639)***	1.085 (0.082)	1.106 (0.101)	1.063 (0.061)	1.040 (0.040)	1.141 (0.132)†
hs-CRP						
NS (n = 117)	0.006 (–5.197)	0.840 (–0.175)	0.991 (–0.009)	0.234 (–1.452)	0.001 (–842.6)	19.198 (2.955)
CS (n = 198)	4.697 (1.547)	4.055 (1.400)	0.119 (–2.131)	0.458 (–0.781)	5.162 (1.641)	15.399 (2.734)

***$p < 0.000$; **$p < 0.01$; *$p < 0.05$; †$p < 0.1$. Waist C., waist circumference; MetS, metabolic syndrome; BDNF, brain-derived neurotrophic factor; NS, non- smoker; CS, current smoker.

its, and neuropeptides levels. A negative correlation was found between food intake and smoking periods (r = –0.237, $p < 0.05$), whereas a positive correlation was found between LeP and the number of cigarettes smoked per day (r = 0.226, $p < 0.05$). In addition, the subjects were subdivided into non-obese (BMI < 25 kg/m^3) and obese (BMI ≥ 25 kg/m^3) groups on the basis of BMI criteria, as suggested in the NCEP-ATP III diagnostic criteria (Asia-Pacific) (2002). The neuropeptide levels of individuals who had never smoked and former and current smokers were compared (Table 4). No differences were found in the concentration of neuropeptides among obese and non-obese groups, according to smoking habits. AdipoN was found to be significantly higher among the non-obese group (BMI < 25 kg/m^3) than the obese group (BMI ≥ 25 kg/m^3) (p = 0.002). However, BDNF and LeP levels were found to be significantly higher in the obese group. Accordingly, multiple logistic regression analysis was performed, with neuropeptides as independent variables and MetS diagnostic indices as dependent variables (Table 5).

In the non-smoking group, triglyceride was significantly associated with AdipoN (odds ratio = 0.660, β value = –0.416, $p < 0.01$) and waist circumference was associated with LeP (odds ratio = 1.622, β value = 0.483, $p < 0.001$). Among current smokers, triglyceride was significantly associated with AdipoN (odds ratio = 0.827, β value = –0.190, $p < 0.05$), waist circumference was associated with LeP (odds ratio = 1.895, β value = 0.639, $p < 0.001$), whereas neuropeptides showed an association with MetS diagnostic indices, although this result was not statistically significant.

DISCUSSION

Some researchers have reported that smoking cessation induces a change in the physiological levels of AdipoN and LeP in the body, and that changes in neuropeptide levels may be associated with the desire to smoke (6,20). In this study, non-smokers were found to have significantly higher

levels of body weight, BMI, waist circumference, and subcutaneous and visceral fat thickness than smokers. In addition, those who had never smoked were found to have better eating habits than current and former smokers. In addition, the results of the serum biochemical analysis showed that non-smokers had a higher LDL-cholesterol level than the other groups ($F = 3.628$, $p = 0.028$) and that former smokers had a higher fasting glucose level than the other groups ($F = 2.642$, $p = 0.073$) (Table 1).

Nicotine binds to the nicotinergic acetylcholine receptors in the γ-aminobutyric acid (GABA), thus affecting the mesolimbic system and sparking a desire to smoke (22). In addition, the mesolimbic system suppresses food consumption and stimulates energy expenditure (23). In the current study, individuals who had never smoked had worse food intake habits than the other groups, such as irregular meals and overeating ($F = 2.303$, $p = 0.049$). In addition, significant differences were found in the levels of anthropometric parameters (body weight, BMI, waist circumference, SFT, and VFT) between smokers and non-smokers. These results suggest that a change in food intake habits occurs due to smoking cessation (24). Nicotine has an influence on endosubstances such as serum glucose, insulin, and lipid (25). This study found different levels of clinical parameters, including insulin and diagnostic indices of MetS, between smokers and non-smokers; these seem related to food intake habits. AdipoN, BDNF, and LeP are neuropeptides contributing towards the balancing regulation of appetite and energy expenditure (26); however, each neuropeptide has a distinct function. AdipoN is a protein contributing towards anti-inflammatory, and is mainly involved in the development and progression of atheroscleroses, glucose metabolism, and weight gain, which is formed in the adipocyte (27). LeP located in the hypothalamic center regulates the sympathetic nerves that contribute towards the metabolic rate, food intake, and the control of body weight (9). Moreover, BDNF is involved in nerve cells and is known to regulate food intake and body weight (7). Some researchers have reported an association between smoking cessation and the physiological levels of AdipoN, BDNF, and LeP (6,19). Otsuka *et al*. (20) reported an increase in plasma AdipoN concentration after smoking cessation. In addition, Lee *et al*. (5) reported an increase in the plasma LeP concentration after smoking cessation. These changes in the concentration of neuropeptides are closely related to gene expression. Iwashma *et al*. (28) reported that nicotine has a direct effect on the mRNA's expression of AdipoN and that the suppression of mRNA's expression of AdipoN reduces the latter's concentration. Li and Kane (18) also reported that Lep mRNA levels decreased significantly in the perirenal and epididymal white adipose tissue of nicotine-treated rats than saline-treated controls, and that plasma Lep concentrations were significantly lower in nicotine-treated rats than the saline-treated controls. In this study, Lep concentration was lower among current smokers, as compared to individuals who had never smoked and former smokers. As mentioned above, these results are considered to be due to nicotine concentration (6). However, the concentration of BDNF among former smokers is 23.6 ± 9.2 pg/ml, which is significantly higher than that of individuals who had never smoked (22.4 ± 5.8 pg/ml) and current smokers (20.4 ± 6.1 pg/ml) ($F = 6.520$, $p = 0.002$) (Table 2). Several studies have reported that BDNF might be associated with nicotine dependence. Kivinummi *et al*. (29) reported that abstinence from chronic nicotine treatment increases BDNF protein levels in the ventral tegmental area, nucleus accumbens, and substantia nigra. Kim *et al*. (19) reported that increased BDNF levels were observed in the plasma of chronic smokers after a two-month smoking cessation period, as compared to baseline levels. One of the important roles played by the BDNF in the midbrain dopaminergic system is to contribute to neuronal repair, differentiation, and survival. These actions are affected by nicotine (30). In this study, higher BDNF levels among former smokers might be due to an increase in the expression of BDNF, occurring as a result of smoking cessation (31,32). Cigarette smoking has been identified as a risk factor for CVD and is associated with insulin resistance and MetS progression (20). To understand mediators and pharmaco-biochemical mechanisms involved in the development and progression of CVD and MetS, it is very important to understand the prevention of these diseases. There are few studies on the relevance of cigarette smoking, cessation, and neuropeptides in relation to these diseases (CVD and MetS). Therefore, we sought to understand the relationship between smoking habits, neuropeptides, and MetS. In this study, LeP had a positive correlation with the amount of smoking ($r = 0.226$, $p < 0.05$), whereas food intake had a negative correlation with smoking period ($r = -0.237$, $p < 0.05$). These results are similar to those of other studies (33). LeP expression increases during the progression of obesity (34); in contrast, AdipoN expression has been shown to decrease as obesity progresses (13).

In this study, no significant change in AdipoN, BDNF, and Lep concentrations were observed within the non-obese group and obese groups. Regardless of smoking habits, while AdipoN level was higher in the non-obese group, BDNF and Lep levels were significantly higher in the obese group (Table 4). Although there is a genetic influence (35), the results allude to an imbalance in food consumption and energy expenditure due to a change in AdipoN, BDNF, and LeP concentration. CVD is closely related to obesity and MetS, and seems to reasonably correlate with neuropeptides (36,37). In this study, multiple logistic regression analysis was performed, with MetS diagnostic indices specified as the dependent variable, as presented in the NCEP-ATP III (Asia-Pacific standard), and AdipoN, BDNF, LeP, and hsCRP specified as the independent variables. As shown in the results, among both smokers and non-smokers, AdipoN

and triglyceride showed a significant negative correlation, whereas LeP and waist circumference showed a significant positive correlation. AdipoN and HDL-cholesterol showed a negative association; however, this result was not statistically significant. In addition, among smokers, BDNF and LeP each correlated with blood pressure and MetS. Zhuo *et al*. (38) also showed that LeP has a positive correlation with the BMI, waist circumference, blood pressure, fasting glucose, and MetS diagnostic indices. That study also showed a negative correlation between LeP and HDL-cholesterol. However, AdipoN was reported to have a negative correlation with LeP. Moreover, it was reported that BDNF has a negative correlation with blood pressure and that hsCRP has a positive correlation with the BMI, waist circumference, body fat, and visceral fat.

In conclusion, cigarette smoking leads to an imbalance of energy expenditure and appetite by changing the concentration of neuropeptides such as AdipoN, BDNF, LeP, and hsCRP. This leads to withdrawal symptoms that, in turn, influence food intake, body weight, the BMI, blood pressure, and abdominal fat; these are risk factors for MetS and CVD.

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