Serum Leptin Levels in Smokers With Type 2 Diabetes

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OBJECTIVE — To elucidate the molecular mechanism of smoking cessation and its relationship to body weight gain, the effects of smoking on the serum levels of leptin were studied in Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — The serum levels of leptin after an overnight fast in 37 adult male Japanese patients with type 2 diabetes (17 smokers and 20 nonsmokers) were assayed using radioimmunoassay. In addition, the serum leptin levels in four nondiabetic smokers were measured before and 2 weeks after quitting smoking.

RESULTS — Smokers and nonsmokers did not differ in age, BMI, or levels of blood glucose and fasting insulin but did differ in HDL cholesterol levels (1.07 ± 0.18 vs. 1.32 ± 0.24 mmol/l for smokers and nonsmokers, respectively, $P = 0.002$). The mean serum leptin level of smokers did not differ from that of nonsmokers (3.8 ± 1.9 vs. 3.8 ± 1.6 ng/ml). The leptin level correlated with the fasting insulin level and BMI ($r = 0.55$ and 0.56, $P < 0.001$ and 0.001, respectively). The leptin levels in four heavy smokers showed no change after the subjects quit smoking (3.3 ± 1.0 vs. 3.8 ± 1.8 ng/ml, before and after quitting, respectively).

CONCLUSIONS — Because smoking did not affect the leptin levels, the effects of quitting smoking on the fuel metabolism appear to be due to some other factors.

Given that smoking is a contributing factor for the development of cardiovascular disease, quitting smoking is a very important factor in the treatment of diabetic patients. However, smoking is associated with reduced body weight in a large-scale monozygotic twin study (1), and the cessation of smoking is known to be an independent contributing factor for body weight gain (2,3). The molecular factors regulating food intake and body weight in smokers, however, are still not understood. Recently, a potent major protein regulating food intake, the leptin gene, has been cloned from an *ob/ob* mouse and a human (4). The plasma concentration of leptin is correlated with the percentage of body fat (5). To evaluate the relationship of leptin to the reduced body weight observed in smokers, middle-aged male patients with type 2 diabetes who had smoked were compared with those who were nonsmokers.

RESEARCH DESIGN AND METHODS

— Thirty-seven Japanese male subjects were randomly recruited from a group of workers for a public transportation company who visited the clinic to undergo an annual health check for type 2 diabetes in 1995. The diagnosis of type 2 diabetes was made according to the World Health Organization's criteria. All subjects were treated with diet therapy. Smokers were defined as subjects who smoked >10 cigarettes per day for ≥2 years. The mean number of cigarettes smoked per day was 27 ± 11. Venous blood samples for blood chemistry were obtained the morning after an overnight fast. The normal HbA_{1c} level measured by high-performance liquid chromatography ranges from 4.0 to 5.7%. Leptin and insulin were assayed using radioimmunoassay (RIA) kits (human leptin RIA kit, Linco Research, St. Charles, MO; and Insulin RIA beads, Dainabot, Tokyo, Japan). In addition, four nondiabetic male volunteers who smoked >20 cigarettes per day volunteered to stop smoking for 2 weeks to study the effect of cessation of smoking on serum leptin levels.

Statistical analysis

All data are expressed as means ± SD. The unpaired and paired Student's *t* tests and the χ^2 test were used to compare differences among the data sets. The correlations among the data sets were investigated by performing a linear regression analysis and a multiple regression analysis. A level of $P < 0.05$ was accepted as statistically significant.

RESULTS

— As shown in Table 1, no differences between smokers and nonsmokers were observed in age, alcohol consumption, family history of diabetes, BMI, blood glucose, HbA_{1c}, fasting insulin, total cholesterol, triglyceride, blood pressure, or individual diabetic complications. Only the HDL cholesterol level was significantly lower in smokers compared with nonsmokers (1.07 ± 0.18 vs. 1.32 ± 0.24 mmol/l, respectively, $P = 0.002$). The mean serum leptin level in smokers was similar to the mean level in nonsmokers (3.8 ± 1.9 vs. 3.8 ± 1.6 ng/ml, NS). In both the smoking and the nonsmoking patients, the serum leptin levels correlated significantly with the BMI ($r = 0.51$ and 0.62, $P = 0.02$ and 0.008, respectively) and with the fasting insulin level ($r = 0.71$ and 0.54, $P = 0.0002$ and 0.02, respectively). Multiple regression analysis revealed both the fasting insulin and BMI to be independent factors contributing to the leptin levels (F value = 15.7 and 10.0, respectively). The mean leptin level in the four male nondiabetic smokers did not change after the 2-week cessation of smoking (3.3 ± 1.0 vs. 3.8 ± 1.8 ng/ml). Also, the BMI did not increase in these subjects during the 2-week cessation of smoking (24.6 ± 4.1 vs. 24.7 ± 4.0 kg/m²).

CONCLUSIONS

— The serum leptin level of the smokers was found to be no

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Abbreviations: RIA, radioimmunoassay.

Table 1—*Comparison of serum leptin levels in smokers and non-smokers with type 2 diabetes*

	Smoker	Non-smoker	*P* value
n	17	20	—
Age (years)	52.2 ± 6.9	55.0 ± 4.9	NS
Alcohol (g/d)	29.0 ± 34.6	37.3 ± 29.5	NS
Family history of diabetes (%)	4(23.5)	5(25)	NS
BMI (kg/m^2)	25.6 ± 3.3	24.7 ± 2.1	NS
Fasting blood glucose (mmol/l)	10.0 ± 2.5	9.4 ± 2.4	NS
2-h postprandial blood glucose (mmol/l)	15.7 ± 5.1	15.9 ± 3.7	NS
HbA_{1c} (%)	8.1 ± 1.7	7.4 ± 1.2	NS
Insulin (U/ml)	7.5 ± 4.5	10.8 ± 11.6	NS
Total cholesterol (mmol/l)	5.66 ± 1.12	5.46 ± 0.84	NS
Triglyceride (mmol/l)	2.22 ± 1.76	1.80 ± 0.73	NS
HDL cholesterol (mmol/l)	1.07 ± 0.18	1.32 ± 0.24	0.002
Systolic blood pressure (mmHg)	130.0 ± 16.5	133.0 ± 17.4	NS
Diastolic blood pressure (mmHg)	81.4 ± 9.9	79.3 ± 9.0	NS
Retinopathy (%)	5 (29.4)	7 (35)	NS
Neuropathy (%)	1 (5.9)	1 (5)	NS
Proteinuria (%)	4 (23.5)	6 (30)	NS
Leptin (ng/ml)	3.82 ± 1.85	3.84 ± 1.56	NS

Data are means ± SD or *n* (%).

higher than that of the age-matched nonsmokers in Japanese male patients with type 2 diabetes. Because the HDL cholesterol level was reduced in smokers compared with nonsmokers, as reported in American industry workers (6), our subjects were thought to reflect the effects of smoking. Furthermore, the cessation of cigarette smoking did not affect the serum leptin level. These findings suggest that smoking does not affect the serum leptin level in Japanese subjects. In a recent paper (7), smokers in Nauru, Mauritius, and Western Samoa demonstrated reduced fasting serum levels of insulin and leptin compared with nonsmokers. Insulin increases the leptin mRNA in cultured adipose cells (8). Correlation between the fasting insulin levels and leptin levels has been reported previously (9). Given that insulin resistance rather than insulin per se regulates the leptin level in humans (10), an enhancement of body fat oxidation by smoking is thus likely to decrease the leptin level through an improvement of insulin resistance or a chronic reduction of the serum insulin level (3). Because our patients had a lower BMI than did subjects in the South Pacific islands (7,11), who, unlike our patients, did not receive diet therapy for type 2 diabetes, the effect of smoking on the serum leptin level through insulin resistance and/or chronic hyperinsulinemia might thus have been neutralized in our patients, although their number may be too small to form any definitive conclusions. Therefore, the mechanism of weight gain after smoking cessation appears to be due to factors other than leptin in Japanese type 2 diabetes patients.

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