

Leptin-to-Adiponectin Ratio as a Potential Atherogenic Index in Obese Type 2 Diabetic Patients

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Obesity promotes the progression of atherosclerosis by inducing multiple cardiovascular and metabolic derangements such as diabetes, hypertension, and dyslipidemia, all of which have high atherogenic potential. Adipose tissue has been considered an important endocrine organ that secretes many biologically active substances, collectively known as adipocytokines (1). Two major adipocytokines, leptin and adiponectin, are thought to play important roles in the regulation of cardiovascular and metabolic homeostasis. Leptin acts directly on the hypothalamus, thereby regulating food intake and energy expenditure (2). Plasma leptin concentrations are significantly elevated in obese subjects in proportion to the degree of adiposity (3), suggesting that hyperleptinemia may play a role in the pathogenesis of obesity-related complications. On the other hand, adiponectin increases tissue fat oxidation, leading to reduced levels of fatty acids and tissue triglyceride content, thus increasing insulin sensitivity (4). Paradoxically, plasma adiponectin concentrations are decreased in obese subjects (5), suggesting that hypoadiponectinemia is involved in the pathophysiology of obesity. Two recent studies have demonstrated that

vascular remodeling and neointimal formation are markedly attenuated in leptin-deficient *ob/ob* mice and *db/db* mice with leptin receptor mutation (6,7), suggesting that leptin may accelerate the development of vascular injury. Conversely, studies with adiponectin-deficient mice have revealed that adiponectin plays a protective role in the development of atherosclerosis (8,9). In obese type 2 diabetic patients who are susceptible to atherosclerosis, plasma concentrations of leptin are increased, whereas those of adiponectin are decreased. We, therefore, hypothesize that the leptin-to-adiponectin ratio serves as an atherogenic index superior to leptin or adiponectin alone. This study was designed to assess the potential of the leptin-to-adiponectin ratio as a biomarker for atherosclerosis in obese type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— A total of 158 Japanese type 2 diabetic patients (69 men and 89 women, mean age 59.8 years) were recruited in our outpatient clinics from April 2003 to May 2004 (Table 1). The study protocol was approved by the ethics committee on human research in Kyoto Medical Center, and all participants gave

written informed consent. The patients had stable and relatively high blood glucose and HbA_{1c} levels ($7.0\% \leq \text{HbA}_{1c} \leq 9.0\%$). They were classified by BMI (nonobese BMI <25.0 and obese BMI ≥ 25.0 kg/m², according to the criteria of the Japan Society for the Study of Obesity) (10); 98 and 60 were defined as nonobese and obese subjects, respectively. There were 39 men and 59 women in the non-obese group and 30 men and 30 women in the obese group. None were receiving insulin, metformin, or thiazolidinediones. Fifty-one nonobese and 25 obese subjects had been treated with sulfonylureas, whereas 47 and 35, respectively, had only been treated with diet.

Fasting plasma glucose, HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels were measured according to standard procedures. Plasma insulin concentration was measured by enzyme immunoassay using a commercially available kit (Tosoh, Tokyo, Japan). Insulin resistance index was assessed by homeostasis model assessment (11). Plasma concentrations of adiponectin and leptin were determined using the respective radioimmunoassay kits (Linco Research, St. Charles, MO). Systolic and diastolic blood pressures were measured twice with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan). Pulse wave velocity (PWV) (12) was determined by an automated multiple pulse wave measurement (ABI-form model: BP-203RPE; Nippon Colin). In this study, PWV was calculated as the mean of the left and right brachial-ankle PWVs, as previously described (13).

Statistical analysis

All statistical analyses were performed using the StatView program version 5.0 for Windows (SAS Institute, Cary, NC). Data are presented as means \pm SE, and $P < 0.05$ was considered statistically significant. Differences among the nonobese and obese subjects were assessed by a two-tailed Student's *t* test. Significance of

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Received for publication 20 March 2004 and accepted in revised form 28 June 2004.

Abbreviations: PWV, pulse wave velocity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Baseline characteristics of the study subjects and Spearman's rank correlation

| Variables | Nonobese (n = 98) | | Obese (n = 60) | | P values | |
|--|-------------------|-------------|--------------------|--------------------|----------|---------|
| | Men | Women | Men | Women | Men | Women |
| n | 39 | 59 | 30 | 30 | | |
| Age (years) | 61.7 ± 1.41 | 60.9 ± 1.04 | 58.0 ± 2.38 | 57.7 ± 2.35 | NS | NS |
| BMI (kg/m ²) | 22.4 ± 0.27 | 21.3 ± 0.29 | 26.6 ± 0.26 | 27.4 ± 0.35 | <0.0001 | <0.0001 |
| PWV (cm/s) | 1667 ± 40 | 1700 ± 34 | 1628 ± 37 | 1634 ± 42 | NS | NS |
| Leptin (ng/ml) | 3.70 ± 0.25 | 5.83 ± 0.33 | 8.90 ± 0.35 | 11.9 ± 0.59 | <0.0001 | <0.0001 |
| Adiponectin (mg/ml) | 4.84 ± 0.25 | 8.25 ± 0.28 | 3.44 ± 0.16 | 5.09 ± 0.30 | 0.0003 | <0.0001 |
| Leptin/adiponectin | 0.85 ± 0.08 | 0.79 ± 0.06 | 2.81 ± 0.17 | 2.59 ± 0.20 | <0.0001 | <0.0001 |
| Spearman's rank correlation (P values) | | | | | | |
| Leptin vs. PWV | −0.060 (NS) | 0.053 (NS) | 0.281 (NS) | 0.315 (NS) | | |
| Adiponectin vs. PWV | 0.079 (NS) | 0.090 (NS) | −0.309 (NS) | −0.122 (NS) | | |
| Leptin/adiponectin vs. PWV | −0.061 (NS) | 0.013 (NS) | 0.378 (P = 0.0420) | 0.390 (P = 0.0356) | | |

Data are means ± SE. NS, not significant. Two-tailed Student's *t* test was used.

correlations for leptin, adiponectin, or leptin-to-adiponectin ratio with PWV was assessed by Spearman's rank correlation analysis.

RESULTS— There were significant differences in BMI, plasma insulin concentration, and the homeostasis model assessment of insulin resistance between the nonobese and obese subjects ($P < 0.0001$), with no significant differences in systolic blood pressure, diastolic blood pressure, fasting plasma glucose, HbA_{1c}, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. In all of the study subjects, leptin, adiponectin, and leptin-to-adiponectin ratio showed no significant correlation with PWV (leptin: $\rho = -0.046$ and $P = 0.5676$, adiponectin: $\rho = 0.094$ and $P = 0.241$, leptin-to-adiponectin ratio: $\rho = -0.066$ and $P = 0.4086$). In the lean subjects (BMI <25 kg/m², $n = 98$), when divided into men and women, there were no significant correlations of leptin, adiponectin, and leptin-to-adiponectin ratio with PWV (leptin: $\rho = 0.062$ and $P = 0.5399$, adiponectin: $\rho = 0.112$ and $P = 0.2715$, leptin-to-adiponectin ratio: $\rho = -0.022$ and $P = 0.8297$). However, in the obese subjects (BMI ≥ 25 kg/m², $n = 60$), leptin-to-adiponectin ratio was positively correlated with PWV ($\rho = 0.308$ and $P = 0.0182$), whereas leptin or adiponectin alone had no correlation (leptin: $\rho = 0.255$ and $P = 0.0505$, adiponectin: $\rho = -0.130$ and $P = 0.3188$). In the male ($n = 30$) and female ($n = 30$) patients in the obese group, leptin-to-adiponectin ratios were positively correlated with PWV (male patients: $\rho = 0.378$ and $P =$

0.0420, female patients: $\rho = 0.390$ and $P = 0.0356$), whereas leptin or adiponectin alone had no correlation in the male and female patients.

CONCLUSIONS— This study represents the first demonstration that in obese type 2 diabetic patients, leptin-to-adiponectin ratio is more strongly correlated with PWV than leptin or adiponectin alone. Since atherosclerosis at necropsy correlates closely with arterial stiffness assessed noninvasively in human and animal studies (12), the data of this study suggest that leptin-to-adiponectin ratio may serve as a potential atherogenic index in obese type 2 diabetic patients. With no significant correlation between leptin-to-adiponectin ratio and PWV in the nonobese subjects, we speculate that the vascular injury seen in these nonobese subjects may be related more strongly with other mechanisms than dysregulated production of adipocytokines. Evidence has suggested that leptin and adiponectin, both of which occur in the adipose tissue, act directly on vascular cells as proatherogenic and antiatherogenic factors, respectively (14,15), implying that they are important mediators linking adiposity and atherosclerosis in the adipovascular axis (9). Collectively, these observations suggest that the leptin-to-adiponectin ratio may serve as a potential atherogenic index in obese type 2 diabetic patients.

Acknowledgments— This work was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan;

by research grants from the Smoking Research Foundation, the Fujisawa Foundation, the Ichiro Kanehara Foundation, the ONO Medical Foundation, AstraZeneca Research (2003), the Mitsui Sumitomo Insurance Welfare Foundation, the Takeda Medical Research Foundation, and the Takeda Science Foundation (to Y.O.); and by Research Grant 13-C5 for Cardiovascular Disease from the Ministry of Health, Labor and Welfare (to N.S.).

We thank Naoki Akamatsu for suggestions regarding statistical analysis.

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