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Smoking is associated with urinary albumin excretion: an evaluation of premenopausal patients with type 2 diabetes mellitus

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Abstract

Cigarette smoking and an increase in urinary albumin excretion are associated with high mortality in patients with type 2 diabetes mellitus. We tested the hypothesis that the presence of a smoking habit correlates with increased urinary albumin excretion in premenopausal Japanese women with type 2 diabetes mellitus. The study consisted of 20 premenopausal Japanese patients with type 2 diabetes mellitus in the current-smokers group (age, 45 ± 4 years, mean ± SD). The control group consisted of 35 age-matched never-smoker patients (age, 45 ± 5 years). Serum triglyceride levels were higher and high-density lipoprotein cholesterol levels were lower in the current-smokers group than in the never-smokers group ($P < .05$ and $P < .01$, respectively). Furthermore, fasting plasma insulin concentrations and the homeostasis model assessment index were higher in the current-smokers group than in the never-smokers group ($P < .005$ and $P < .001$, respectively). Urinary albumin excretion also was higher in the current-smokers group than in the never-smokers group ($P < .0001$). Multivariate logistic analysis revealed that urinary albumin excretion is independently associated with current smoking in Japanese premenopausal with type 2 diabetes mellitus (odds ratio, 1.79; 95% confidence interval, 1.08-3.87; $P < .01$). The results of this study show that current smoking is associated with an increased level of urinary albumin excretion, suggesting that smoking was a risk factor in the development of increased urinary albumin excretion in these patients.
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1. Introduction

Cigarette smoking is a recognized risk factor for cardiovascular disease, stroke, and renal dysfunction [1-4]. Microalbuminuria, a slight increase in urinary albumin excretion due to increased glomerular permeability, in patients with type 2 diabetes mellitus is similarly associated with an increased risk of cardiovascular morbidity and mortality [5].

Compared to male smokers, female smokers have an approximately 50% higher relative risk of developing myocardial infarction and also have a relatively higher mortality rate due to vascular disease [6,7]. Most of these studies, however, did not independently evaluate men and women, and most of the women were postmenopausal.

Of interest, these smoking-related gender differences were more pronounced when only women younger than 45 years were considered [8]. Moreover, the smoking rate has been shown to be increasing in young women, and cigarette smoking is clearly the most important risk factor for acute thrombosis and sudden coronary death [9]. These observations suggest a distinct role for smoking in the risks of cardiovascular disease for women, with menopause and the level of estrogen playing major roles in atherogenesis [10,11].

Despite the common association with an increased risk for cardiovascular disease, the association between current smoking and urinary albumin excretion in premenopausal women with type 2 diabetes mellitus has not been adequately investigated. Therefore, we have designed the present study to test for this association. To this end, we compared the levels of urinary albumin excretion, echocardiographs, and the metabolic profiles of current-smoker and never-smoker Japanese premenopausal women with type 2 diabetes mellitus, and then evaluated which of

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the parameters were risk factors for current smoking in these patients.

2. Subjects and methods

2.1. Patients

One hundred seventy-eight Japanese female patients with type 2 diabetes mellitus that were admitted to our department between January 2003 and December 2005 were screened. Ninety-four patients (n = 29 in the smokers group, average age, 61 years; n = 65 in the never-smokers group, average age, 62 years) were postmenopausal and were excluded from this study. The remaining 84 patients did not have organic heart disease as determined by a physical examination, smoking habits, a chest x-ray, 12-lead electrocardiography, echocardiography, and a treadmill-exercise electrocardiography, and were enrolled in this study. None of the patients were pregnant or taking estrogen/progesterone contraceptives.

Table 1
Clinical characteristics of the patients in this study

	Never smokers	Current smokers	*P*
Age (y)	45 ± 5	45 ± 4	NS
No. of women	35	20	NS
BMI (kg/m^2)	25.9 ± 6.3	26.8 ± 6.3	NS
Brinkman index	0	443 ± 187	<.0001
Duration of diabetes (y)	4.5 ± 2.9	5.0 ± 3.5	NS
Hypertension (%)	40	45	NS
Dyslipidemia (%)	34	40	NS
Drug use (%)			
Sulfonylurea	31	35	NS
α-Glucosidase inhibitors	23	25	NS
Pioglitazone	3	5	NS
Statin	29	35	NS
Calcium channel antagonists	34	35	NS
β-Blockers	9	10	NS
ACE inhibitors	11	15	NS
Angiotensin receptor blocker	29	35	NS
SBP (mm Hg)	127 ± 21	131 ± 18	NS
DBP (mm Hg)	79 ± 13	81 ± 10	NS
HR (beats/min)	69 ± 8	71 ± 11	NS
T-cho (mg/dL)	196 ± 34	207 ± 39	NS
TGL (mg/dL)	119 ± 41	152 ± 53	.0150
HDL-C (mg/dL)	53 ± 12	44 ± 8	.0022
FPG (mg/dL)	141 ± 23	151 ± 28	NS
F-IRI (μU/mL)	5.6 ± 1.6	6.8 ± 1.3	.0049
HOMA index	1.9 ± 0.6	2.6 ± 0.7	.0007
HbA_{1c} (%)	7.6 ± 1.2	7.7 ± 1.0	NS
UA (mg/dL)	5.4 ± 1.5	6.4 ± 1.2	.0090
Crn (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	NS
Ccr (mL/min)	114 ± 26	103 ± 20	NS

Data are presented as mean ± SD. BMI indicates body mass index; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; T-cho, total cholesterol; TGL, triglycerides; FPG, fasting plasma glucose; F-IRI, fasting immunoreactive insulin; UA, uric acid; Crn, creatinine, Ccr, creatinine clearance; NS, not significant.

To determine the level of urinary albumin excretion, urine was collected for 3 consecutive days. The level of urinary albumin excretion was measured in the urine samples collected during 24-hour periods by immunoturbidimetry (TIA MicroAlb Kit, Nittobo, Tokyo). The urinary albumin excretion rates are expressed in milligrams expected per 24hours. The 24-hour levels of urinary albumin excretion for each patient are presented as the mean values from 3 consecutive measurements. The accuracy of this methods has previously been validated [12] Twenty-nine of the 84 enrolled patients were excluded from further evaluation because of extenuating circumstances: 13 of the excluded patients had macrolabuminuria (≥300 mg/24 hours), 14 subjects were being treated with insulin, and 2 patients had angina pectoris.

Therefore, 55 of the original 84 patients (mean age, 45 ± 5 years; age range, 36-52 years) were selected for this study. Twenty (23.8%) of the 55 patients were current smokers, and the other 35 age-matched premenopausal patients were never smokers.

The clinical characteristics of both the current-smokers and never-smokers groups are summarized in Table 1. All patients underwent clinical examinations to exclude the presence of secondary hypertension. Essential hypertension was defined by diastolic blood pressure of 90 mm Hg or higher, systolic blood pressure of 140 mm Hg or higher, or self-reported use of antihypertensive medication [13]. The 14 never-smoker patients and 9 current-smoker patients who met our criteria were being treated with calcium channel antagonists, β-blockers, angiotensin-converting enzyme inhibitors, and/or angiotensin II receptor blockers. Dyslipidemia was defined as fasting triglyceride levels of 200 mg/dL or greater or high-density lipoprotein cholesterol (HDL-C) less than 45 mg/dL for women and HDL [13]. Eight of the 20 patients in the current-smokers group and 12 of 35 patients of the never-smokers group met the criteria for dyslipidemia.

All subjects gave their written informed consent to participate in the study, and the study protocol was approved by the ethics committee of the Oita University Hospital.

2.2. Smoking habits

Patients were categorized as having a smoking habit when they smoked at least one cigarette per day. The smoking status was expressed by the Brinkman index, which is calculated as the number of cigarettes per day multiplied by the number of years the patient had been smoking [14].

2.3. Insulin resistance

Insulin resistance was evaluated by the homeostasis model assessment (HOMA) index: (fasting plasma insulin [μU/mL] × fasting plasma glucose [mmol/L])/22.5 [15].

2.4. Statistical analysis

All data are presented as means ± SD. Differences between groups were examined with Student *t* tests. Categorical variables were compared by using χ^2 analysis.

Multiple logistic regression analysis was used to assess the combined influence of variables on the smoking habit. Hypertension, diabetes mellitus, and dyslipidemia were represented by dummy variables (male = 1, female = 0; presence = 1, absence = 0) in the logistic regression analysis. A value of P less than .05 was considered statistically significant.

3. Results

As shown in Table 1, the mean ages of the 2 groups were similar. No significant differences were observed between the 2 groups with respect to body mass index and duration since the onset of diabetes. The percentages of patients with hypertension, dyslipidemia, and administered medications were similar between the 2 groups. As expected, the average Brinkman index was higher in the current-smokers group than in the never-smokers group ($P < .0001$).

The hemodynamic data listed in Table 1, including the resting systolic and diastolic blood pressures, heart rate, total plasma cholesterol, creatinine levels, and creatinine clearance rates, were not significantly different between the 2 groups. With regard to lipid metabolism, plasma triglycerides were higher and HDL-C was lower in the current-smokers group than in the never-smokers group ($P = .0150$ and $P = .0022$, respectively). The fasting plasma insulin concentration, the HOMA index values, and uric acid levels were higher in the current-smokers group than in the never-smokers group ($P = .0049$, $P = .0007$, and $P = .0090$, respectively). There were no significant differences between the 2 groups in the fasting plasma glucose concentration or the amount of glycosylated hemoglobin (HbA_{1c}).

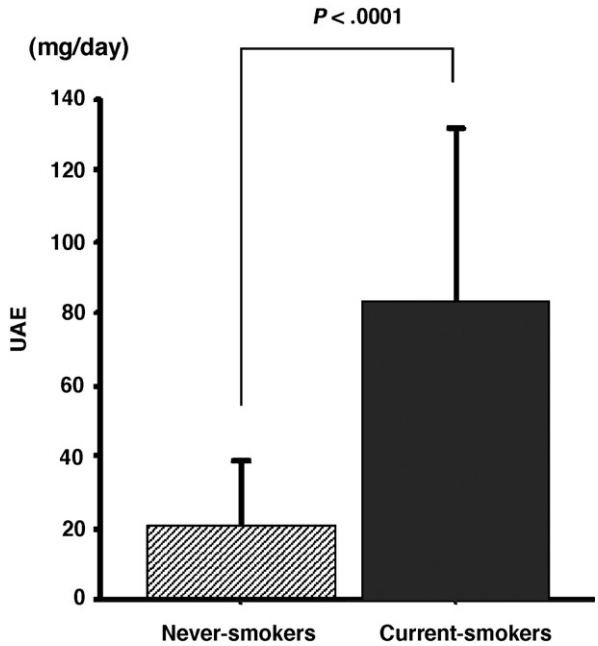

Fig. 1. A comparison of the urinary albumin excretion (UAE) of never-smoker and current-smoker patients with type 2 diabetes mellitus. Data are means ± SD.

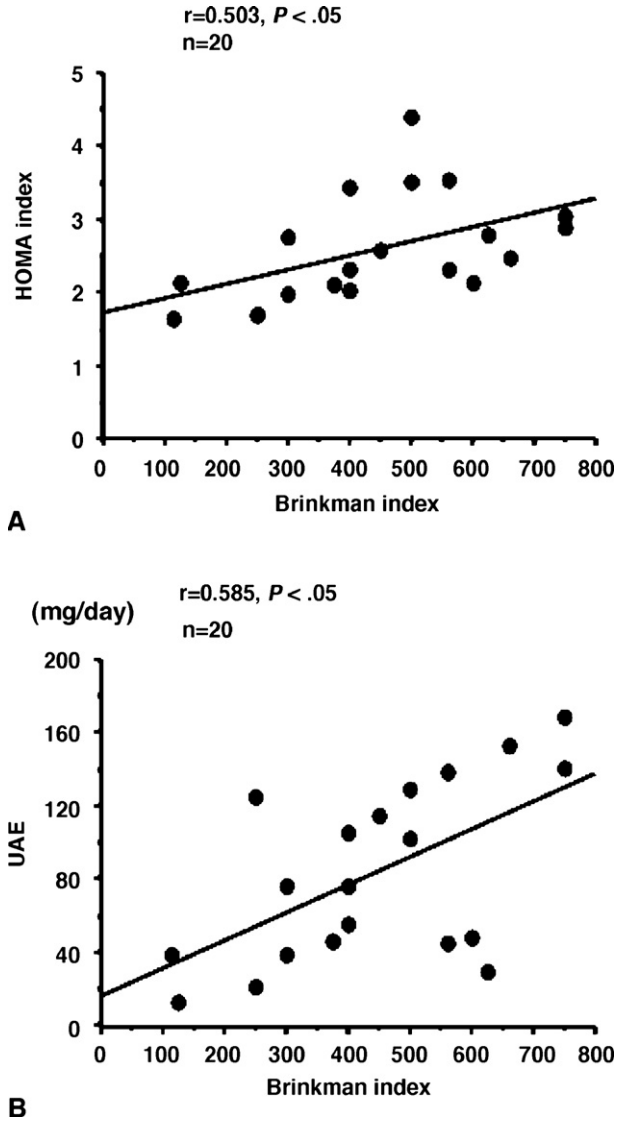

Fig. 2. Correlations between the Brinkman index and either the HOMA index (A) or urinary albumin excretion (UAE, B) in the current smokers with type 2 diabetes mellitus.

Fig. 1 shows that urinary albumin excretion was higher in the current-smokers group than in the never-smokers group (83.0 ± 48.8 vs 20.6 ± 17.8 mg/d; $P < .0001$).

Fig. 2 shows that the HOMA index and the level of urinary albumin excretion were significantly correlated with the Brinkman index ($r = 0.585$, $P = .0137$ and $r = 0.503$, $P = .0221$, respectively) in current-smoker patients with type 2 diabetes mellitus.

In univariate logistic regression analysis, smoking was associated with triglyceride levels (odds ratio [OR], 1.02; 95% CI, 1.00-1.03; $P = .0211$), HDL-C levels (OR, 0.91; 95% CI, 0.85-0.97; $P = .0054$), the fasting plasma insulin concentration (OR, 1.77; 95% CI, 1.16-2.71; $P = .0084$), the HOMA index (OR, 4.91; 95% CI, 1.73-17.6; $P = .0039$), uric acid levels (OR, 1.75; 95% CI, 1.12-2.73; $P = .0137$), and urinary albumin excretion (OR, 2.38; 95% CI, 1.05-5.34; $P = .0007$). These dependent metabolic parameters in the

Table 2
Univariate logistic regression analysis: the dependent variables in current-smoker patients with type 2 diabetes mellitus

	Current smokers		
	OR	95% CI	*P*
Age	1.04	0.92-1.16	NS
BMI	1.02	0.94-1.12	NS
Duration of diabetes	1.04	0.87-1.25	NS
Hypertension	1.40	0.41-4.79	NS
Dyslipidemia	1.63	0.49-5.44	NS
SBP	1.01	0.98-1.04	NS
DBP	1.01	0.97-1.06	NS
HR	1.02	0.94-1.06	NS
T-cho	1.01	0.99-1.03	NS
TGL	1.02	1.00-1.03	.0211
HDL-C	0.91	0.85-0.97	.0054
FPG	1.02	0.99-1.04	NS
F-IRI	1.77	1.16-2.71	.0084
HOMA index	5.50	1.73-17.6	.0039
HbA_{1c}	1.06	0.63-1.78	NS
UA	1.75	1.12-2.73	.0137
UAE	2.38	1.05-5.34	.0007
Crn	3.65	0.89-18.9	NS
Ccr	0.98	0.96-1.01	NS

UAE indicates urinary albumin excretion. See Table 1 for other abbreviations. Significant predictors of smoking were identified among the parameters including hypertension (absent = 0, present = 1) and dyslipidemia (absent = 0, present = 1).

premenopausal women with type 2 diabetes mellitus are listed in Table 2.

Multivariate logistic regression analysis revealed an independent association between an increased level of urinary albumin excretion and current smoking (OR, 1.79; 95% CI, 1.08-3.87; $P = .0091$) in the premenopausal women with type 2 diabetes mellitus.

4. Discussion

In our present study, the metabolic parameters and serum triglyceride levels were higher, whereas HDL-C was lower, in the current-smokers group than in the never-smokers group. In addition, fasting plasma insulin, the HOMA index, and uric acid levels were higher in the smokers group than in the never-smokers group. Urinary albumin excretion was also higher in the current-smokers group than in the never-smokers group. Furthermore, multiple logistic regression analyses revealed that urinary albumin excretion was a risk factor for current smoking in Japanese premenopausal women with type 2 diabetes mellitus.

Previous reports demonstrated that smoking rates for all adult men and women in Japan were 43.3% to 67.8% and 10.2%, respectively [16,17]. Watts [18] reported that smoking rate among young Japanese women in their late teens and early 20s has risen to about 15%. Moreover, 1 in 4 Japanese teenagers is a smoker. In the present study, the prevalence of smoking was 36.3% (20 of 55) in premenopausal women with type 2 diabetes mellitus, which was about 3 times higher than the smoking rate in the general population.

Studies of patients with type 1 and type 2 diabetes mellitus show that smoking is an independent risk factor for the development of microalbuminuria [19,20]. Chase et al [19] reported that in a group of 359 young subjects with type 1 diabetes mellitus the prevalence of borderline and elevated urinary albumin excretion rates was 2.8-fold higher in smokers than nonsmokers. Similarly, the risk of microalbuminuria in the first months after the diagnosis of type 2 diabetes mellitus was increased for current smokers; in a study that included 85 patients with newly diagnosed type 2 diabetes mellitus, the OR for the presence of microalbuminuria was 26.3 for current smokers compared with only 3.42 for a 1% increase in the level of HbA_{1c} [20].

Several studies have shown that smoking is associated with increased insulin resistance and other metabolic abnormalities. Dzien et al [21] reported that smoking was associated with a metabolic profile (elevated fasting glucose, triglyceride, and HDL-C levels) that indicated a higher degree of insulin resistance in nondiabetic men. Recently, we have reported that smoking is associated with abnormal cardiac autonomic function and insulin resistance in type 2 diabetic patients [22].

How did smoking increase the urinary albumin excretion as observed in this study? Although we cannot determine the underlying cause in this type of cross-sectional study, we do have 2 hypotheses for this observation.

First, the plasma concentration of endothelin has been shown to be higher in smokers compared with nonsmokers [23]. Interestingly, additional evidence for functional and structural changes in the glomeruli of patients with type 2 diabetes mellitus who smoked were reported [24]. In this study, 96 patients underwent kidney biopsies that clearly showed significant changes in the glomeruli and basal membranes of the smokers, results that correspond to impairment of the glomerular filtration rate.

Second, there are several reports that show smoking is associated with insulin resistance [25,26] in healthy volunteers and patients with type 2 diabetes mellitus. Laakso et al [27,28] demonstrated that subjects who were insulin resistant, including obese and type 2 diabetic patients, exhibited blunted insulin-mediated vasodilation and impaired endothelium-mediated vasodilation. It was suggested that endothelial dysfunction may be an integral component of insulin resistance, independent of hyperglycemia. Thus, it is logical to hypothesize that the impaired endothelial function observed in the patients with type 2 diabetes mellitus with microalbuminuria may be caused by severe insulin resistance. Given the vital roles of the endothelium and nitric oxide in the reduction of vascular tone, platelet aggregation and adhesion, smooth muscle cell proliferation and migration, thrombosis, and leukocyte adhesion [29], it follows that more severely impaired endothelium-dependent vasodilation may be, at least in part, responsible for the increased incidence of macrovascular disease observed in patients with type 2 diabetes

mellitus with microalbuminuria. In addition, the degree of insulin resistance was also positively correlated with tobacco consumption and with serum cotinine levels in long-term users of nicotine gum (cotinine is a metabolite of nicotine, and serum or urine levels of cotinine are considered to reflect the degree of nicotine use) [30]. Furthermore, we have previously discussed the involvement of endothelial dysfunction in the development of microalbuminuria and depressed cardiovascular autonomic dysfunction [31]. In fact, in a recent report demonstrating the association between smoking and microalbuminuria, the authors stressed the central role of endothelial dysfunction in such an interaction [32]. It is therefore logical to hypothesize that the impaired endothelial function observed in the patients with type 2 diabetes mellitus with microalbuminuria may be caused by endothelial dysfunction associated with smoking and insulin resistance. This hypothesis was supported by the present findings that the Brinkman and HOMA index values were significantly associated in the current smokers.

To our knowledge, this is the first report that demonstrates that smoking was a risk factor for development of urinary albumin excretion in Japanese premenopausal women with type 2 diabetes mellitus.

The present study, however, has some limitations. First, although an increase in urinary albumin excretion and insulin resistance has been demonstrated in dipper patients compared with nondipper patients [33,34], ambulatory blood pressure monitoring was not performed in this study and, therefore, the association among smoking, microalbuminuria, and dipper/nondipper status was not evaluated in our study. Second, estrogen, the predominant female sex hormone, facilitates vascular vasodilatation by several mechanisms, including direct [35] and indirect [36] actions on vascular endothelial and smooth muscle cells that appear to result from the activation of estrogen receptors in the vessel wall [37]. We did not measure endothelial function or the levels of the related vasoactive substrates, including estrogen, endothelin, prostacyclin, and nitric oxide [38]. Finally, given the high smoking rate among Japanese men and the much higher risk for cardiovascular complications in postmenopausal women, one could argue that the present study should have included these populations. Toward this point, we examined these populations in a recent study and reported that smoking is associated with cardiac autonomic dysfunction and insulin resistance in type 2 diabetic middle-aged men and postmenopausal women [22]. In conclusion, the present results demonstrate that in Japanese premenopausal type 2 diabetic patients, current smoking is associated with increased urinary albumin excretion, suggesting that smoking was a risk factor in the development of the increased urinary albumin excretion in these patients.

The prognostic value of smoking cessation for decreased urinary albumin excretion in premenopausal patients with type 2 diabetes mellitus should be further evaluated.

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References

[1] Jonas MA, Oates JA, Ockene JK, et al. Statement on smoking and cardiovascular disease for health care professionals: American Heart Association. Circulation 1992;86:1664-9.
[2] Price JF, Mowbray PI, Lee AJ, et al. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery study. Eur Heart J 1999;20:344-53.
[3] Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factor for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2616-22.
[4] Ejerblad E, Fored CM, Lindblad P, et al. Association between smoking and chronic renal failure in a nationwide population-based case-control study. J Am Soc Nephrol 2004;15:2178-85.
[5] Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non–insulin-dependent diabetes mellitus: a systematic overview of the literature. Arch Intern Med 1997;157:1413-8.
[6] Prescott E, Hippe M, Schnohr P, et al. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998;316:1043-6.
[7] Prescott E, Osler M, Andersen PK, et al. Mortality in women and men in relation to smoking. Int J Epidemiol 1998;27:27-32.
[8] Njolstad I, Arnesen E, Lund-Larsen PG. Smoking, serum lipids, blood pressure, and sex differences in myocardial infarction. A 12-year follow-up of the Finnmark Study. Circulation 1996;93:450-6.
[9] Burke AP, Farb A, Malcolm GT, et al. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation 1998;97:2110-6.
[10] Colditz GA, Willet WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316:1105-10.
[11] Van der Schouw YT, Van der Graaf Y, Steyerberg EW, et al. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714-8.
[12] Taniwaki H, Nishizaki Y, Kawagishi T, et al. Decrease in glomerular filtration rate in Japanese patients with type 2 diabetes is linked to atherosclerosis. Diabetes Care 1998;21:1848-55.
[13] Liao D, Sloan RP, Cascio WE, et al. Multiple metabolic syndrome is associated with lower heart rate variability. The Atherosclerosis Risk in Communities Study. Diabetes Care 1998;21:2116-22.
[14] Brinkman GL, Coates O. The effects of bronchitis, smoking and occupation on ventilation. Ann Rev Respir Dis 1963;87:68-93.
[15] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
[16] Ishizuka N, Ishizuka Y, Toda E, et al. Association between cigarette smoking, metabolic syndrome, and carotid arteriosclerosis in Japanese individuals. Atherosclerosis 2005;18:381-8.
[17] Japanese Ministry of Health, Labour and Welfare. National nutrition survey in Japan, 2002, Tokyo. 222-225, 2003 (in Japanese with English summary).
[18] Watts J. Japan steps up fight against tobacco industry. Antismoking lobby fights for public's hearts, lung, and minds. Lancet 2003;362:304.
[19] Chase HP, Garg SK, Marshall G, et al. Cigarette smoking increases the risk of albuminuria among subjects with type 1 diabetes. JAMA 1991;265:614-7.
[20] Keller CK, Bergis KH, Fliser D, et al. Renal findings in patients with short-term type 2 diabetes. J Am Soc Nephrol 1996;7:2627-35.
[21] Dzien A, Dzien-Bischinger C, Hoppichler F, et al. The metabolic syndrome as a link between smoking and cardiovascular disease. Diabetes Obes Metab 2004;6:127-32.

[22] Anan F, Takahashi N, Shinohara T, et al. Smoking is associated with insulin resistance and cardiovascular autonomic dysfunction in type 2 diabetic patients. Eur J Clin Invest 2006;36:459-65.
[23] Gambaro G, Verlato F, Budakovic A, et al. Renal impairment in chronic cigarette smokers. J Am Soc Nephrol 1998;9:562-7.
[24] Baggio B, Budakovic A, Vestra MD, et al. Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. J Am Soc Nephrol 2002;13:2730-6.
[25] Facchini FS, Hollenbeck CB, Jeppesen JJ, et al. Insulin resistance and cigarette smoking. Lancet 1992;339:1128-30.
[26] Targher G, Alberiche M, Zenere MB, et al. Cigarette smoking and insulin resistance in patients with non–insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1997;82:3619-24.
[27] Laakso M, Edelman SV, Brechtel G, et al. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. A novel mechanism for insulin resistance. J Clin Invest 1990;85:1844-52.
[28] Laakso M, Edelman SV, Brechtel G, et al. Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. Diabetes 1992;41:1076-83.
[29] Lloyd-Jones DM, Bloch KD. The vascular biology of nitric oxide and its role in atherogenesis. Annu Rev Med 1996;47:365-75.
[30] Eliasson B, Taskinen MR, Smith U. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. Circulation 1996;94:878-81.
[31] Takahashi N, Anan F, Nakagawa M, et al. Microalbuminuria, cardiovascular autonomic dysfunction, and insulin resistance in patients with type 2 diabetes mellitus. Metabolism 2004;53:1359-64.
[32] Orth S. Effects of smoking on systemic and intrarenal hemodynamics: influence on renal function. J Am Soc Nephrol 2004;15:S58-S63.
[33] Bianchi S, Bigazzi R, Baldari G, et al. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. Am J Hypertens 1994;7:23-9.
[34] Anan F, Takahashi N, Ooie T, et al. Role of insulin resistance in nondipper hypertensive patients. Hyperens Res 2003;26:669-76.
[35] Russell KS, Haynes MP, Sinha D, et al. Human vascular endothelial cells contain membrane binding sites for estradiol, which mediate rapid intracellular signaling. Proc Natl Acad Sci U S A 2000;97:5930-5.
[36] Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med 1991;325:1196-204.
[37] Losordo DW, Kearney M, Kim EA, et al. Variable expression of the estrogen receptor in normal and atherosclerotic coronary arteries of premenopausal women. Circulation 1994;89:1501-10.
[38] Kiowski W, Linder L, Stoschitzky K, et al. Diminished vascular response to inhibition of endothelium-derived nitric oxide and enhanced vasoconstriction to exogenously administered endothelin-1 in clinically healthy smokers. Circulation 1994;90:27-34.