Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1099–1103
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Metabolic syndrome, insulin resistance, and atherosclerosis in Japanese type 2 diabetic patients

Ataru Taniguchi[a,d,*], Mitsuo Fukushima[b], Akira Kuroe[a], Kenji Sakaguchi[a], Hiroko Hashimoto[a], Ikuko Yoshioka[a], Naomi Kitatani[a], Tomoko Tsuji[a], Michihiro Ohya[a], Minako Ohgushi[a], Shoichiro Nagasaka[c], Okihisa Isogai[d], Yoshikatsu Nakai[e], Nobuya Inagaki[f], Yutaka Seino[a]

[a]*Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka 553-0003, Japan*
[b]*Department of Health Informatics Research, Translational Research Informatics Center, Foundation for Biochemical Research and Innovation, Kobe 650-0047, Japan*
[c]*Department of Endocrinology and Metabolism, Jichi Medical School of College, Tochigi 700-0045, Japan*
[d]*Isogai Medical Clinic, Osaka 532-0003, Japan*
[e]*Karasuma-Oike Nakai Clinic, Kyoto 604-0845, Japan*
[f]*Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan*

Received 28 January 2006; accepted 28 July 2006

Abstract

The aim of the present study was to investigate the relationships between metabolic syndrome and atherosclerosis in 57 Japanese type 2 diabetic patients. Metabolic syndrome was diagnosed based on the criteria raised by the Japan Internal Medicine Society. Insulin resistance was estimated by the insulin resistance index of homeostasis model assessment. Ultrasonographically measured carotid atherosclerosis, brachial-ankle pulse wave velocity (ba-PWV), and ankle brachial index (ABI) were used to assess the degree of atherosclerosis. Of 57 patients, 25 were diagnosed as having metabolic syndrome. The patients with metabolic syndrome had significantly higher levels of waist circumference, insulin, insulin resistance index of homeostasis model assessment, systolic and diastolic blood pressures, and serum triglycerides, and lower concentrations of adiponectin. However, there was no significant difference in age, sex, glycosylated hemoglobin (hemoglobin A_{1c}), fasting glucose, leptin, and tumor necrosis factor system activities including tumor necrosis factor α between the 2 groups. Furthermore, no significant difference was observed in the degree of carotid atherosclerosis (intimal-medial thickness in plaque-free segments: 0.72 ± 0.03 vs 0.72 ± 0.02 mm, $P = .435$; carotid stenosis in plaque segments: 6.6% ± 3.0% vs 6.6% ± 1.7%, $P = .497$), ba-PWV (1676 ± 56 vs 1654 ± 44, $P = .380$), and ABI (1.16 ± 0.01 vs 1.15 ± 0.01, $P = .245$) between the 2 groups. From these results, it can be suggested that metabolic syndrome, an insulin-resistant state, is not associated with carotid atherosclerosis, ba-PWV, or ABI in Japanese type 2 diabetic patients.

1. Introduction

Type 2 diabetes mellitus is a heterogeneous syndrome characterized by insulin resistance and/or defective insulin secretion [1]. There seems to be ethnic difference in insulin resistance in type 2 diabetes mellitus. Using a minimal model approach shown by Bergman [2] and Welch et al [3], we previously demonstrated that 40% of type 2 diabetic patients are insulin resistant in Japanese populations [4-6]. In contrast, Haffner et al [7] used this approach and found that 92% of type 2 diabetic patients are insulin resistant in white populations. Moreover, mean body mass index (BMI) in representative epidemiological studies of Japanese type 2 diabetic patients were 23 to 25 kg/m^2, lower than that found in the studies of the whites [8]. Whereas it is well recognized that BMI is one of the most important factors contributing to insulin resistance in diabetic patients, this unique feature of Japanese type 2 diabetic patients allows us to explore other factors related to insulin resistance.

Taking into account these fascinating features, we previously demonstrated that serum triglycerides is independently associated with insulin resistance in Japanese type 2 diabetic patients [9,10]. Thereafter, we found that

* Corresponding author. Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka-city, Osaka 553-0003, Japan. Fax: +81 6 6458 6994.
E-mail address: taniguchi.ataru@a5.kepco.co.jp (A. Taniguchi).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.07.027

adiponectin and leptin are also independent factors associated with insulin resistance [11,12]. Moreover, we showed that both triglyceride and adiponectin are associated with visceral fat areas, whereas leptin is associated with subcutaneous fat areas in these patients [11-13]. Thus, abdominal fat areas are likely to be associated with insulin resistance in Japanese type 2 diabetic patients. Not only triglyceride but also leptin and adiponectin are recognized to be associated with atherosclerosis in diabetic patients [14-16].

The metabolic syndrome is reported to be one of the conditions associated with insulin resistance and/or atherosclerosis in humans [17]. The major criteria for the metabolic syndrome, however, are emphasized on the waist circumference. Waist circumference provides a crude but effective measure of visceral fat [18]. Along with increased waist circumference, the minor criteria for the metabolic syndrome such as raised triglyceride/low high-density lipoprotein (HDL) cholesterol, high blood pressure, or high concentration of glucose are suggested to be associated with atherosclerosis in Japanese type 2 diabetic patients. Thus, it may be questioned whether the use of metabolic syndrome to assess atherosclerosis is superior to other risk factors such as hyperglycemia especially in Japanese type 2 diabetic patients. It has been established that hyperglycemia per se is associated with the development of atherosclerosis in diabetic patients. To clarify this, we recruited Japanese type 2 diabetic patients who had no major evidence of atherosclerosis to compare the degree of atherosclerosis between the diabetic patients with and without metabolic syndrome syndrome, taking into account BMI and hemoglobin A_{1c} (HbA_{1c}).

2. Subjects and methods

Fifty-seven Japanese type 2 diabetic patients with BMI of less than 27 kg/m^2 who were well controlled in terms of glycosylated hemoglobin (HbA_{1c}) (7.1% ± 0.1%, mean ± SEM) were enrolled. Type 2 diabetes mellitus was diagnosed based on the World Health Organization criteria [19]. They had no evidence of current acute illness including clinically significant infectious disease. The duration of diabetes was 10.9 ± 1.0 years (range, 1-35 years). Of 57 diabetic patients, 52 were taking sulfonylureas and the rest were treated with diet alone. They had not been treated with insulin or any medications known to alter insulin sensitivity. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease (CVD). Patients did not consume alcohol or perform heavy exercise for at least 1 week before the study.

Metabolic syndrome was diagnosed by the criteria raised by the Japan Internal Medicine Society. Although the use of waist circumference to assess abdominal adiposity is superior to BMI, the cutoff value for waist circumference is likely to be population-specific as there are clear differences across ethnic populations in the relationship between overall adiposity, abdominal adiposity, and visceral fat accumulation. The major criterion in Japanese population is waist circumference of greater than 85 cm in men and greater than 90 cm in women. The minor criteria is as follows: serum triglyceride of ≧150 mg/dL or HDL cholesterol of <40 mg/dL, blood pressure of ≧130/85 mm Hg, and fasting glucose concentration of ≧110 mg/dL. The patients who had both 1 major criteria and 2 or 3 minor criteria were diagnosed as having metabolic syndrome.

Blood was drawn in the morning after a 12-hour fast. Plasma glucose was measured with a glucose oxidase method. The triglycerides, total cholesterol, and HDL cholesterol were also measured. Serum insulin was measured using a 2-site immunoradiometric assay (Insulin Riabead II, Dainabot, Japan). Coefficients of variation were 4% for insulin of greater than 25 μU/mL and 7% for insulin of less than 25 μU/mL, respectively. Serum adiponectin and leptin were measured with a radioimmunoassay kit (Linco Research, St Charles, MO). The intra- and interassay coefficients of variation (CVs) were less than 5% for adiponectin and leptin, respectively. Serum tumor necrosis factor α (TNF-α) concentrations were measured with an enzyme immunoassay kit (Quantikine HS Human TNF-α Immunoassay Kit, R&D Systems, Minneapolis, MN), and serum concentrations of soluble TNF receptor 1 (sTNF-R1) and soluble TNF receptor 2 (sTNF-R2) were measured with an enzyme-linked immunosorbent assay (BIOTRAK, Amersham Life Sciences, Uppsala, Sweden), as described previously [20]. The limits of sensitivity for TNF-α, sTNF-R1, and sTNF-R2 were 0.5, 25, and 50 pg/mL, respectively. The intra-assay CVs for TNF-α, sTNF-R1, and sTNF-R2 were 5.9%, 4.7%, and 3.2%, respectively. The interassay CVs for TNF-α, sTNF-R1, and sTNF-R2 were 10.8%, 5.8%, and 3.6%, respectively. Samples for insulin, adiponectin, leptin, and TNF were prepared, frozen, and stored at −70°C until the assay.

The estimate of insulin resistance index of homeostasis model assessment (HOMA-IR) was calculated with the formula: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 [21]. The insulin resistance index of homeostasis model assessment was validated in diabetic patients treated with diet therapy alone and in those treated with sulfonylureas [22,23]. Therefore, we estimated HOMA-IR in diet-treated and sulfonylurea-treated diabetic patients.

Along with ultrasonographically measured carotid atherosclerosis, brachial-ankle pulse wave velocity (ba-PWV) and ankle brachial index (ABI) were used to assess the degree of atherosclerosis.

A carotid sonography was performed with high-resolution B-mode scanning equipment (Logic 500 GE Yokogawa, Milwaukee, WI) with a 7.5-MHz sector scanner probe [24]. The common carotid arteries of both sides were examined with longitudinal and transverse scans because we could not analyze the internal and external carotid arteries fully in all

patients. The CV for interobserver variability was found to be 8.5% and the CV for intraobserver variability was 6.0%. The intimal-medial thickness (IMT) of the common carotid artery was measured in plaque-free segments as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The mean of IMT in plaque-free segments of bilateral common carotid arteries was used for the analysis. The degree of stenosis was also measured in the plaque segments of bilateral common carotid arteries. It was calculated as a percentage ratio between the area of the plaque and that of the lumen using the formula: (lumen area − residual lumen area)/lumen area × 100. Both the areas were automatically measured by the system on a frozen transverse scanning plane at the site of maximal narrowing. When 2 or more plaques were present in the vessel, only that causing the greatest degree of stenosis was considered for analysis.

Brachial-ankle PWV and ABI were measured using a volume-plethysmographic apparatus (from PWV/ABI version-112, Colin, Komaki, Japan). Briefly, after an overnight fast, the subjects were examined in the supine position, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. The characteristic points of waveforms were determined automatically, and the results were printed out. All procedures took about 5 minutes. The interobserver and intraobserver variation coefficients were 8.4% and 10.0%, respectively. Measurements on different days revealed that slight changes in blood pressure did not correlate with changes in ba-PWV. The mean ba-PWV and ABI values measured on either side of each patient were used for the analysis.

2.1. Data analysis

Data were presented as means ± SEM. Statistical analysis was conducted using the StatView 5 system (Statview, Berkeley, CA). The means of 2 groups were compared using Student t test. $P < .05$ was considered as significant.

3. Results

The subjects studied were all Japanese type 2 diabetic patients (40 men and 18 women) with an age range of 43 to 79 years (62.7 ± 1.1 years) and a BMI of 17.1 to 26.7 kg/m^2 (23.0 ± 0.3 kg/m^2). The fasting plasma glucose was 143 ± 3 mg/dL and HbA_{1c} was 7.1% ± 0.1%. Fasting insulin level was 6.8 ± 0.4 μU/mL. Serum triglycerides and total and HDL cholesterol levels were 119 ± 7, 208 ± 5, and 61 ± 2 mg/dL, respectively. Serum adiponectin and leptin concentrations were 13.6 ± 1.2 μg/mL and 5.8 ± 0.5 ng/mL, respectively. The concentrations of TNF-α, sTNF-R1, and sTNF-R2 were 3.1 ± 0.2, 1132 ± 36, and 2009 ± 54 pg/mL, respectively. On the other hand, there was a wide variation in insulin resistance calculated from HOMA-IR in our diabetic patients (range, 0.71-6.10; 2.40 ± 0.16). Of 57 patients, 24 (41%) patients had HOMA-IR of greater than 2.5, indicating that they are insulin resistant [9,10]. Intimal-medial thickness in plaque-free segments of carotid artery, carotid stenosis in plaque segments, ba-PWV, and ABI were 0.72 ± 0.02 mm (range, 0.40-1.10 mm), 6.6% ± 1.6% (range, 0%-54.5%), 1664 ± 35 cm/s (range, 1139-2294 cm/s), and 1.15 ± 0.01 (range, 1.02-1.26), respectively.

Table 1 shows the clinical profile between the patients with and without metabolic syndrome. Of the 57 patients, 25 were diagnosed as having metabolic syndrome. These patients had significantly higher levels of waist circumference, HOMA-IR, systolic and diastolic blood pressures, and serum triglycerides, but significantly lower concentrations of adiponectin as compared with those without metabolic syndrome. No significant difference was observed in age, sex, fasting glucose, leptin, and HbA_{1c} between the two. The concentrations of TNF-α, sTNF-R1, and sTNF-R2 were not significantly different between the 2 groups. There was no significant difference in the degree of carotid atherosclerosis (IMT in plaque-free segments: 0.72 ± 0.03 vs 0.72 ± 0.02 mm, $P = .435$; carotid stenosis in plaque segments: 6.6% ± 3.0% vs 6.6% ± 1.7%, $P = .497$), ba-PWV (1676 ± 56 vs 1654 ± 44, $P = .380$), and ABI (1.16 ± 0.01 vs 1.15 ± 0.01, $P = .245$) between the 2 groups.

Table 1
Clinical characteristics of the diabetic patients included in the study

	Metabolic syndrome (+)	Metabolic syndrome (−)	P
No. of subjects	25	33	–
Waist (cm)	89.6 ± 0.8	77.3 ± 1.2	<.001
Age (y)	62.1 ± 1.8	63.2 ± 1.3	.316
Male/female	20/5	20/12	.071
HOMA-IR	2.71 ± 0.23	2.17 ± 0.20	<.05
Diabetes duration (y)	10.3 ± 1.4	11.1 ± 1.4	.351
Smoking (%)	20	21	.486
SU/diet	22/3	29/3	.343
BMI (kg/m^2)	24.0 ± 0.4	22.2 ± 0.4	<.001
Systolic blood pressure (mm Hg)	143 ± 3	133 ± 3	<.05
Diastolic blood pressure (mm Hg)	88 ± 2	81 ± 2	<.005
Fasting glucose (mg/dL)	141 ± 4	145 ± 4	.237
Fasting insulin (μU/mL)	7.7 ± 0.6	6.1 ± 0.6	<.05
HbA_{1c} (%)	7.0 ± 0.2	7.2 ± 0.2	.227
Triglycerides (mg/dL)	134 ± 12	108 ± 9	<.05
Total cholesterol (mg/dL)	208 ± 7	207 ± 7	.473
HDL cholesterol (mg/dL)	57 ± 3	63 ± 3	.062
LDL cholesterol (mg/dL)	131 ± 6	127 ± 6	.347
adiponectin (μg/mL)	10.7 ± 1.1	15.5 ± 1.9	<.05
Leptin (ng/mL)	6.2 ± 0.8	5.4 ± 0.7	.242
TNF-α (pg/mL)	3.4 ± 0.3	2.9 ± 0.2	.065
sTNF-R1 (pg/mL)	1118 ± 46	1143 ± 52	.366
sTNF-R2 (pg/mL)	1971 ± 68	2036 ± 78	.276
IMT (mm)	0.72 ± 0.03	0.72 ± 0.02	.435
Stenosis (%)	6.6 ± 3.0	6.6 ± 1.7	.497
ba-PWV (cm/s)	1676 ± 56	1654 ± 44	.380
ABI	1.16 ± 0.01	1.15 ± 0.01	.245

SU indicates sulfonylurea; LDL indicates low-density lipoprotein.

4. Discussion

Type 2 diabetes mellitus is a syndrome characterized by insulin resistance and/or defective insulin secretion [1]. There seems to be ethnic difference in insulin resistance in type 2 diabetes mellitus. Haffner et al surveyed the prevalence of white type 2 diabetic patients and found that 92% of type 2 diabetic patients were insulin resistant [7]. Chaiken et al [25] reported that 60% of type 2 diabetic patients with BMI of less than 30 kg/m^2 were insulin resistant in African American populations. We recently demonstrated that 40% of type 2 diabetic patients are insulin resistant in Japanese type 2 diabetic patients [9,10]. Thus, Japanese type 2 diabetic patients are considered to have a unique feature, specifying that they are divided into 2 categories: one with insulin resistance and the other with normal insulin sensitivity [4-6,9,10]. This idea was reconfirmed in the present study.

Another unique feature of Japanese type 2 diabetic patients is that they are not always massively obese. We previously showed that the mean BMI in representative epidemiological studies of Japanese type 2 diabetic patients are 23 to 25 kg/m^2, lower than in the studies of other ethnic populations such as whites [8]. Thus, Japanese type 2 diabetic patients are hypothesized to have another fascinating feature in terms of insulin resistance and atherosclerosis as compared with other ethnic populations.

In the present study, we first found that metabolic syndrome is associated with insulin resistance but not always associated with atherosclerosis in Japanese type 2 diabetic patients. This is a surprising finding because it is a commonly held belief that metabolic syndrome is an important cluster of metabolic abnormalities linked with insulin resistance and CVD [17].

One possible explanation is that the waist circumference, the major criteria for the metabolic syndrome, might not be an accurate measure of intra-abdominal fat areas in Japanese type 2 diabetic patients who are not massively obese. Fujimoto et al [26] previously demonstrated that visceral adiposity, blood pressure, and plasma glucose, but not abdominal circumference, are independent risk factors for incident coronary heart disease in Japanese-American diabetic patients. The BMI of their patients (25.8 kg/m^2) was similar to that of our patients.

The second possible explanation is because of the clinical characteristics or to the degree of atherosclerosis in our patients. The patients studied had no significant CVD and were not accompanied by any major significant abnormalities in the ultrasonographically measured carotid atherosclerosis, PWV, and ABI. The range of IMT, carotid stenosis, PWV, and ABI were 0.4 to 1.1 mm, 0% to 54.5%, 1139 to 2294 cm/s, and 1.02 to 1.26, respectively. Therefore, the association between metabolic syndrome and the degree of atherosclerosis would probably be higher in a population-based study in which the patients with CVD were included in this study.

The third possible explanation is that inflammation including TNF-α and/or hyperglycemia rather than insulin resistance may have unfavorable effects on the atherosclerotic change in Japanese type 2 diabetic patients. It is reported that high glucose can activate monocytes and induce the expression of TNF-α via oxidant stress and nuclear factor–κB transcription factor [27]. Shai et al [28] demonstrated that sTNF-R2 is strongly associated with the risk of coronary heart disease in patients with type 2 diabetes mellitus. Rauchhaus et al [29] demonstrated that elevated sTNF-R1 has shown to be predictive of cardiovascular mortality in patients with chronic heart failure. We recently found that sTNF-R1 was associated with albuminuria in Japanese type 2 diabetic patients [30]. In the present study, we could not find any significant differences in TNF-α system activities (TNF-α, sTNF-R1, sTNF-R2) between the 2 groups. It should be noted that TNF-α system activities are not associated with insulin resistance in Japanese type 2 diabetic patients with BMI of less than 27.0 kg/m^2 [20]. Alternatively, the long-standing diabetic state per se is such a powerful factor on atherosclerosis so that the effect of other risk factors including metabolic syndrome is masked. This idea is supported by the results from the recent 11-year follow-up investigation shown by Bruno et al [31] that diabetic patients with metabolic syndrome had similar all-cause and CVD mortality as compared with those without metabolic syndrome.

Irrespective of this, our present study showed that metabolic syndrome, an insulin-resistant state, is not associated with carotid atherosclerosis, ba-PWV, or ABI in Japanese type 2 diabetic patients. In this respect, Kahn et al [32] very recently warns that clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the metabolic syndrome.

References

[1] Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity (review). Endocr Rev 1998;19:491-503.
[2] Bergman RN. Toward physiological understanding of glucose tolerance: minimal-model approach. Diabetes 1989;38:1512-27.
[3] Welch S, Gebhart SSP, Bergman RN, Phillips LS. Minimal model analysis of intravenous glucose tolerance test–derived insulin sensitivity in diabetic subjects. J Clin Endocrinol Metab 1990;71:1508-18.
[4] Taniguchi A, Nakai Y, Fukushima M, Kawamura H, Imura H, Nagata I, et al. Pathogenic factors responsible for glucose tolerance in patients with NIDDM. Diabetes 1992;41:1540-6.
[5] Nagasaka S, Tokuyama K, Kusaka I, Hayashi H, Rokkaku K, Nakamura T, et al. Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable-labeled minimal model approach. Diabetes 1999;48:1054-60.
[6] Taniguchi A, Nakai Y, Tokuyama K, Sakai M, Doi K, Fukushima M, et al. Role of glucose effectiveness in the evolution of NIDDM. In: Berman RN, Lovejoy JC, editors. The minimal model approach and determinants of glucose tolerance, vol. 7. Louisiana State University Press; 1997. p. 357-67.
[7] Haffner SM, D'Agostino Jr R, Mykkanen L, Tracy R, Howard B, Rewers M, et al. Insulin sensitivity in subjects with type 2 diabetes:

relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. Diabetes Care 1999;22:562-8.

[8] Fukushima M, Usami M, Ikeda M, Nakai Y, Taniguchi A, Suzuki H, et al. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 2004;53:831-5.

[9] Taniguchi A, Fukushima M, Sakai M, Kataoka K, Nagata I, Doi K, et al. The role of the body mass index and triglyceride levels in identifying insulin-sensitive and insulin-resistant variants in Japanese non–insulin-dependent diabetic patients. Metabolism 2000;49:1001-5.

[10] Taniguchi A, Fukushima M, Sakai M, Miwa K, Makita T, Nagata I, et al. Remnant-like particle cholesterol, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. Diabetes Care 2000;23:1766-9.

[11] Yatagai T, Nagasaka S, Fukushima M, Taniguchi A, Nakamura T, Kuroe A, et al. Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in subjects with type 2 diabetes mellitus. Metabolism 2003;52:1274-8.

[12] Okumura T, Taniguchi A, Nagasaka S, Sakai M, Fukushima M, Kuroe A, et al. Relationship of regional adiposity to serum leptin level in nonobese Japanese type 2 diabetic male patients. Diabetes Metab 2003;29:15-8.

[13] Taniguchi A, Nakai Y, Sakai M, Yoshii S, Hamanaka D, Hatae Y, et al. Relationship of regional adiposity to insulin resistance and serum triglyceride levels in nonobese Japanese type 2 diabetic patients. Metabolism 2002;51:544-8.

[14] Fontbonne A, Eschwege E, Cambien F, Richard JL, Ducinetiere P, Thibult N, et al. Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes: results from the 11-year follow-up of the Paris Prospective Study. Diabetologia 1989;32:300-4.

[15] Shinada K, Miyazaki T, Daida H. Adiponectin and atherosclerotic disease. Clin Chim Acta 2004;344:1-12.

[16] Wallace AM, McMahon AD, Packard CJ, MIBiol AK, Shepherd J, et al. Plasma leptin and the risk of cardiovascular disease in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 2001;104:3052-6.

[17] Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2002;24:683-9.

[18] Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460-8.

[19] World Health Organization. Diabetes mellitus: report of a WHO study group. Geneva: World Health Org; 1985 [Tech. Rep. Ser., no. 727].

[20] Ohya M, Taniguchi A, Fukushima M, Nakai Y, Kawasaki Y, Nagasaka S, et al. Three measures of tumor necrosis factor-alpha activity and insulin resistance in non-obese Japanese type 2 diabetic patients. Metabolism 2005;54:1297-301.

[21] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

[22] Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 2000;23:57-63.

[23] Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Kawagichi T, et al. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 1999;22:818-22.

[24] Taniguchi A, Nishimura F, Murayama Y, Nagasaka S, Fukushima M, Sakai M, et al. *Porphyromonas gingivalis* infection is associated with carotid atherosclerosis in non-obese Japanese type 2 diabetic patients. Metabolism 2003;52:142-5.

[25] Chaiken RL, Banerji MA, Pasmantier RM, Huey H, Hirsch S, Lebovitz HE. Patterns of glucose and lipid abnormalities in black NIDDM subject. Diabetes Care 1991;14:1036-42.

[26] Fujimoto WY, Bergstrom RW, Boyko EJ, Chen K-W, Leonetti DL, Newell-Morris L, et al. Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. Diabetes Care 1999;22:1808-12.

[27] Guha M, Bai W, Nadler J, Natarajan BR. Molecular mechanisms of alpha gene expression in monocytic cells via hyperglycemia-induced oxidant stress dependent and independent pathways. J Biol Chem 2000;275:17728-35.

[28] Shai I, Schulze MB, Manson JE, Rexrode KM, Stampfer MJ, Mantzoros C, et al. A prospective study of soluble tumor necrosis factor-α receptor II (sTNF-RII) and risk of coronary heart disease among women with type 2 diabetes. Diabetes Care 2005;28: 1376-82.

[29] Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 2000;102:3060-7.

[30] Kawasaki Y, Taniguchi A, Fukushima M, Nakai Y, Kuroe A, Ohya M, et al. Soluble TNF receptors and albuminuria in non-obese Japanese type 2 diabetic patients. Horm Metab Res 2005;37:617-21.

[31] Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, et al. Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes. The Casale Monferrato Study. Diabetes Care 2004;27:2689-94.

[32] Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the study of diabetes. Diabetes Care 2005;28:2289-304.