Table 1—*Patient prevalence at baseline, age-adjusted HRs with 95% CIs, and incidence of CHD, stroke, or both in 1,424 Japanese patients with type 2 diabetes (771 men and 653 women) according to individual cardiovascular risk factors comprising the metabolic syndrome as defined by the International Diabetes Federation* (b, c, *and* d *include specific treatment for each abnormality*)

	Prevalence at baseline (%)		HR for CHD		HR for stroke		HR for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
a) Waist circumference ≥85 cm (men), ≥90 cm (women)	36.7	9.7	1.68 (0.92–3.08)	1.13 (0.26–4.86)	0.91 (0.44–1.86)	1.11 (0.31–4.05)	1.32 (0.83–2.10)	1.13 (0.43–2.97)
b) Triglycerides ≥150 mg/dl	26.5	23.4	2.93 (1.55–5.53)	2.03 (0.81–5.04)	1.10 (0.51–2.36)	0.59 (0.20–1.78)	1.96 (1.21–3.19)	1.13 (0.56–2.26)
c) HDL cholesterol <40 mg/dl (men), <50 mg/dl (women)	19.3	36.3	1.82 (0.94–3.54)	1.48 (0.63–3.49)	0.99 (0.41–2.40)	1.34 (0.61–2.94)	1.53 (0.90–2.61)	1.34 (0.74–2.40)
d) SBP ≥130 mmHg or DBP ≥85 mmHg	64.1	68.8	1.04 (0.53–2.01)	1.05 (0.39–2.84)	2.08 (0.90–4.82)	1.63 (0.60–4.37)	1.29 (0.77–2.17)	1.29 (0.64–2.59)
a plus one or more of *b*, *c*, or *d*	32.0	9.2	1.72 (0.94–3.15)	1.15 (0.27–4.90)	1.14 (0.56–2.34)	1.13 (0.31–4.11)	1.47 (0.91–2.35)	1.14 (0.44–3.01)

DBP, diastolic blood pressure; SBP, systolic blood pressure.

drome] vs. 8.1 [without metabolic syndrome] in men; 5.8 vs. 5.5 in women) or stroke (8.1 vs. 7.5 in men; 8.8 vs. 7.0 in women) did not differ significantly between subjects with or without metabolic syndrome. Age-adjusted HRs were calculated to determine whether the new metabolic syndrome definition or its components could predict cardiovascular events (Table 1). Patients diagnosed as having metabolic syndrome, even when subgrouped by therapeutic contents (oral hypoglycemic agents or insulin use), did not show significantly raised HRs for CHD, stroke, or both compared with subjects without metabolic syndrome. However, male patients with raised triglyceride levels and/or having specific treatment for this condition had a significantly increased risk of CHD (HR 2.93, $P < 0.001$) and combined CHD and stroke (1.96, $P = 0.006$), regardless of whether they had metabolic syndrome (Table 1).

CONCLUSIONS— Our previous analysis (1) showed that HRs for CVD in patients with WHO-defined metabolic syndrome were significantly elevated compared with HRs in subjects without metabolic syndrome (although the HR for CHD in male patients was not elevated). Diagnosis of metabolic syndrome by the NCEP definition was less predictive but still associated with a significantly elevated HR for CHD in male patients. However, metabolic syndrome diagnosis by the new definition was not predictive for CVD in either male or female patients in the same prospective setting. Therefore, the new definition did not improve the prediction of adverse cardiovascular events, and its clinical usefulness in Japanese diabetic patients is rather less than that of the existing definitions or of hypertriglyceridemia alone in male patients.

The indispensability of central obesity to the new definition was a major cause of the decrease in the prevalence of metabolic syndrome observed using the new definition. The fact that most patients with central obesity were classified as having metabolic syndrome revealed that metabolic syndrome diagnosis by the new definition was highly dependent on waist circumference when applied to Japanese diabetic subjects. It also denoted that most patients with central obesity had at least one other cardiovascular risk factor, suggesting a close relationship between central obesity and other cardiovascular risk factors. However, this combination was not necessarily associated with an increased risk of CVD in our patients. This latter observation led us to further evaluate the significance of waist circumference in our patients by modifying the threshold within the 65- and 105-cm range and recalculating the HRs. Interestingly, we could not find any thresholds associated with significantly elevated HRs for cardiovascular events in either male or female subjects (data not shown). Therefore, the new definition's lower prediction power for CVD seemed to be derived from the indispensability of the waist circumference component.

To date, prospective trials examining the significance of metabolic syndrome as a predictor of CVD in diabetic patients (1,6–9) have been inadequate (10,11). Many important issues remain to be resolved. *1*) Is the new definition of metabolic syndrome a good predictor of CVD in diabetic patients of differing ethnicities (12)? 2) Are there any other combinations of components (or different thresholds) that are better predictors of CVD in Asian diabetic patients (13–15)? 3) Is the concept of metabolic syndrome truly applicable or relevant to diabetic patients in general? Investigations of these issues would aid the screening of diabetic patients at especially high risk of CVD, as well as inform and direct ethnic group–specific management of diabetes (16–19).

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Case report

Diabetic lipemia with eruptive xanthomatosis in a lean young female with apolipoprotein E4/4

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Abstract

Eruptive xanthomas in adults are usually indicative of chylomicronemia. Although diabetes mellitus is the most common secondary cause of chylomicronemia, which is designated as diabetic lipemia, the clinical characteristics of diabetes with regard to development of xanthomas are not well defined. In this paper, we describe a young female who displayed eruptive xanthomas as an initial manifestation of diabetic lipemia. The patient was a 20-year-old female with a body mass index of 18.9 kg/m^2 and Marfanoid appearance. Her past history was unremarkable, except for patent ductus arteriosus and mild mental retardation. She was admitted to our division for eruptive xanthomas on the extremities and marked hyperglycemia (random glucose, 520 mg/dl) and hypertriglyceridemia (6880 mg/dl). She was diagnosed with Type 2 diabetes based on the positive family history of diabetes, residual secretory capacity of insulin, and absence of autoantibodies related to Type 1 diabetes. Based on the increase in the concentrations of both chylomicrons and very low density lipoproteins, type V hyperlipoproteinemia was diagnosed. After the initiation of insulin therapy, both hypertriglyceridemia and eruptive xanthomas subsided, without administering any hypolipidemic agents. Minimal model analysis of a frequently sampled intravenous glucose tolerance test revealed severe insulin resistance, despite the absence of obesity. Post-heparin lipoprotein lipase (LPL) activity was moderately decreased, and common mutations in the LPL gene were not demonstrated by genetic screening. The apolipoprotein E phenotype was E4/4, which is known to be associated with type V hyperlipoproteinemia. Hypoadiponectinemia of 1.7 μg/ml was also revealed, which may, in part, account for the insulin resistance and decreased LPL activity. In conclusion, the clustering of apolipoprotein E4/4 and hypoadiponectinemia, in addition to insulin resistance and poor glycemic control, might have resulted in hypertriglyceridemia with eruptive xanthomatosis in this subject.

Keywords: Diabetic lipemia; Hypertriglyceridemia; Chylomicronemia; Apolipoprotein E; Eruptive xanthoma; Insulin resistance; Adiponectin

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1. Introduction

Eruptive xanthomas in adults are usually indicative of chylomicronemia with triglyceride levels greater than 2000 mg/dl [1]. Genetic defects, such as lipoprotein lipase (LPL) deficiency, and/or secondary disturbances in the triglyceride metabolism can result in chylomicronemia. Although diabetes mellitus is the most common secondary cause of type V hyperlipoproteinemia, a type of chylomicronemia, few reports are available on the precise characteristics of the diabetic patients who display eruptive xanthomas and hypertriglyceridemia. In this paper, we report the case of a young female patient who displayed eruptive xanthomas as an initial manifestation of diabetes mellitus and hypertriglyceridemia. The peculiar characteristics of this patient included a Marfanoid appearance, severe insulin resistance, and hypoadiponectinemia, despite the absence of obesity and apolipoprotein E4/4 phenotype. In order to define the clinical characteristics of diabetic patients who display eruptive xanthomas, the relationship between eruptive xanthomas and diabetes mellitus was also investigated by reviewing the relevant literature.

2. Material and methods

2.1. Case report

The patient was a 20-year-old Japanese female with mild mental retardation. Her past history was unremarkable with the exception of a surgery for patent ductus arteriosus at the age of 10 years. At that time, the serum levels of total cholesterol and triglyceride were 141 and 74 mg/dl, respectively. She did not consume alcohol or tobacco. The family history revealed that her maternal grandfather, maternal aunt, and mother had diabetes mellitus. Her mother died of acute myocardial infarction at the age of 51 years; she had undergone hemodialysis for chronic renal failure due to diabetic nephropathy. She had also undergone bilateral lower limb amputations. The patient's father died of pancreatic cancer at the age of 47 years. Her elder brother had verbal disability and mental retardation. In these subjects, past history of hyperlipidemia was unremarkable, and data on plasma lipids were not available. There was no consanguineous marriage in this pedigree.

On December 28, 2001, the patient observed a number of yellow papules surrounded by moderate red halo spreading on the dorsal surface of both hands. Within a few days, these papules spread to the extensor surface of forearms, upper arms, and thighs. She complained of moderate pruritus on the dorsal surface of the hands, but was otherwise asymptomatic and had no abdominal pain. On investigating, a local physician detected marked hyperglycemia (random glucose of 520 mg/dl) and hyperlipidemia with serum triglyceride and total cholesterol levels of 6880 and 901 mg/dl, respectively. She was referred to the hospital for further evaluation and admitted to the author's division on January 10, 2002.

The patient's profile was as follows: height, 159.5 cm; weight, 48 kg; body mass index, 18.9 kg/m^2; and blood pressure, 128/90 mmHg. Diabetic retinopathy, lipemia retinalis, and ectopia lentis were not observed. Examination of the neck, chest, and abdomen revealed no abnormal findings, except for a scar on the chest. A cardiac echogram did not show any valvular or aortic abnormalities. Several non-confluent yellow papules, 2–5 mm in diameter, with erythematous halos, were observed on the dorsal surface of the hands, extensor surface of the forearms, upper arms, and thighs (Fig. 1). Similar lesions were not observed on the trunk and buttocks. The patellar and Achilles tendon reflexes and the sense of vibration in the legs were normal. The arm span was 163 cm, which was greater than her height. Arachnodactyly was observed; however, no extreme extensibility in the joints of the extremities was observed.

Routine laboratory examination (Table 1) revealed increased levels of fasting plasma glucose (FPG) and HbA_{1c} along with mildly elevated levels of ketone bodies and free fatty acid (FFA); however, blood gas analysis did not reveal metabolic acidosis. The serum total cholesterol and triglyceride levels were extremely increased, and an overnight incubation of her serum revealed the presence of chylomicrons. Serum high density lipoprotein (HDL) cholesterol level, measured by a homogenous assay (polyethylene glycol-modified enzyme/α-cyclodextrin sulfate assay, Kyowa Medex, Tokyo, Japan), was as high as 69 mg/dl despite severe hypertriglyceridemia. However, it is likely that the level was overestimated because this

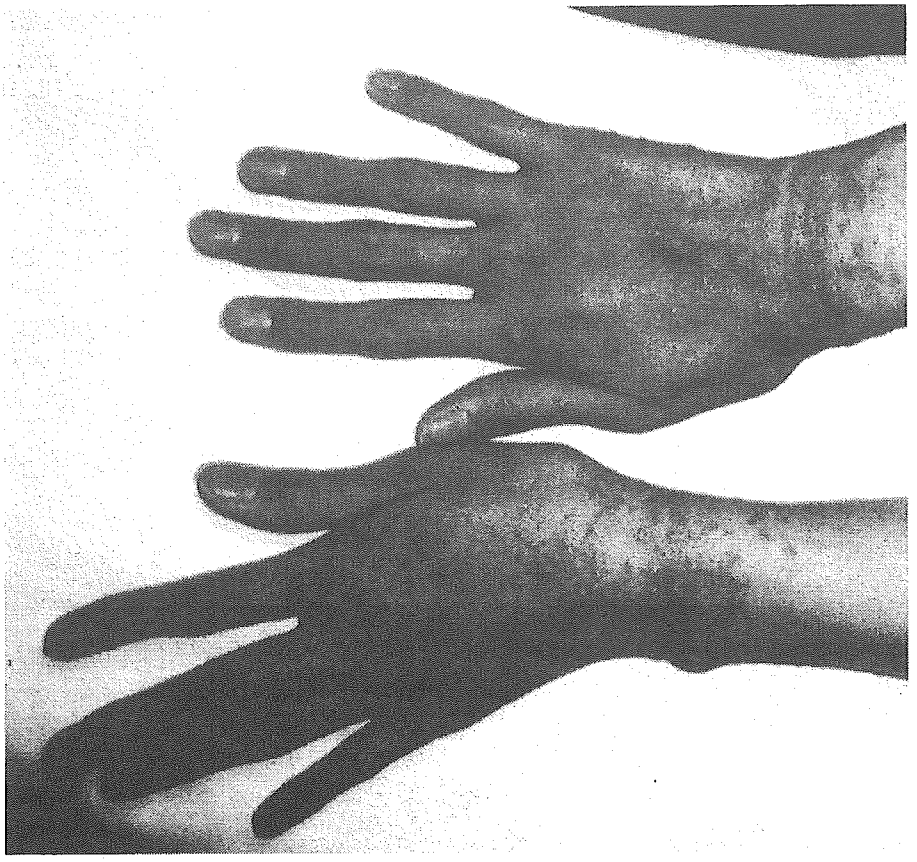

Fig. 1. Eruptive xanthomas on the dorsal surface of the hands. Note the presence of arachnodactyly.

assay has been shown to cross-react, in part, with the fractions of chylomicrons and very low density lipoprotein (VLDL) [2]. Serum amylase concentration was within the normal reference range, and no evidence of pancreatitis was observed on an abdominal echogram. Serum and urinary C-peptide levels were moderately decreased, and both anti-glutamic acid decarboxylase (GAD) and anti-insulinoma-associated protein 2 (IA-2) antibodies (measured using commercial RIA kits; Cosmic Corporation, Tokyo, Japan) were negative. Thyroid function tests revealed decreased levels of free T_3 and T_4, with normal TSH level; this was suggestive of a non-thyroidal illness.

On the next day after admission (Day 2), detailed analysis of serum lipids was performed (Table 2). Prior to these examinations, insulin was not administered. Quantification of serum total lipoproteins, measured by a heparin-$CaCl_2$ precipitation method (BLF "Eiken," Eiken Chemical, Tokyo, Japan), revealed a marked increase in chylomicrons and VLDL and a moderate increase in low density lipoprotein (LDL); this was indicative of type V hyperlipoproteinemia. Remnant-like lipoprotein particle cholesterol (RLP-C) level was also elevated. Apolipoprotein C2, C3, and E levels were markedly increased, and the apolipoprotein E phenotype was E4/4. Quantification of LPL mass, measured 10 min after an intravenous injection of heparin (30 U/kg body weight), revealed that it was within the normal reference range, and the post-heparin LPL activity was moderately decreased. Hepatic triglyceride lipase (HTGL) activity was within the normal reference range.

Regarding the adipocytokines, the serum leptin concentration of 5.5 ng/ml, measured by a radioimmunoassay kit (Linco Research Inc., St. Charles, MO), was appropriate for her BMI [3]. Serum tumor necrosis factor α level, measured by an enzyme-linked immunosorbent assay (ELISA) kit (Japan Immunor-

Table 1
General laboratory findings on admission

Urinalysis		Biochemistry		Endocrinology	
Protein	2+	TP	7.8 g/dl	Total ketone bodies	1462 μM
Sugar	3+	Albumin	4.5 g/dl	AcAc	232 μM
Urobilinogen	±	BUN	9 mg/dl	3-OHBA	1230 μM
Bilirubin	−	Cr	0.21 mg/dl	FFA	1.60 mEq/l
Ketone body	3+	UA	4.1 mg/dl		
Hematology		T-Bil	0.31 mg/dl	Serum C-peptide	
WBC	6500/μl	ALP	104 mU/ml	Fasting	0.9 ng/ml
RBC	419×10^4/μl	AST	8 mU/ml	Post-prandial	2.8 ng/ml
Hb	14.2 g/dl	ALT	4 mU/ml	Urine C-peptide	17.3 μg/day
Ht	37.7%	LDH	453 mU/ml		
Plt	12.5×10^4/μl	γ-GTP	39 mU/ml	Anti-GAD antibody	<0.3 U/ml
Blood gas analysis		Amylase	57 mU/ml	IA-2 antibody	<0.1 U/ml
pH	7.382	T-Chol	953 mg/dl		
P_{CO_2}	43.3 mmHg	HDL-Chol	69 mg/dl	TSH	2.10 μU/ml
P_{O_2}	73.5 mmHg	TG	4538 mg/dl	Free T_3	1.14 pg/ml
HCO_3^-	25.2 mmol/l	FPG	350 mg/dl	Free T_4	0.61 ng/dl
BE	0.0 mmol/l	HbA_{1c}	15.7%		

esearch Laboratories, Takasaki, Japan), was less than 5 pg/ml. Serum high-molecular weight adiponectin concentration, measured by a specific ELISA kit (Fujirebio, Tokyo, Japan), was as low as 1.7 μg/ml as compared to 9.0 ± 6.1 μg/ml in the more obese Type 2 diabetic female patients ($n = 12$; BMI, 22.0 ± 4.0 kg/m^2; mean ± S.D.).

Histopathological examination of the biopsy specimen of the eruptions on the extensor surface of the forearm was consistent with eruptive xanthoma, showing multiple infiltrating foamy histiocytes (Fig. 2).

After the analysis of lipid abnormalities, insulin therapy was introduced, and the dose of insulin was gradually increased (Fig. 3). Finally, a total of 42 units of premixed insulin (Penfill-30R, Novo Nordisk Pharma, Tokyo, Japan) was administered daily; this decreased the pre- and post-prandial glucose levels to

Table 2
Detailed analysis of serum lipids

	Day 2 (on admission)	Day 23	Normal range
Chylomicron	6350	84	<30 mg/dl
VLDL	3080	436	<210 mg/dl
LDL	800	995	190–580 mg/dl
RLP-C	606.9	ND	<7.5 mg/dl
Lp (a)	3	ND	<40 mg/dl
Apolipoprotein A1	99	89	126–165 mg/dl
Apolipoprotein A2	21.4	20.1	24.6–33.3 mg/dl
Apoipoprotein B	218	165	66–101 mg/dl
Apolipoprotein C2	78.8	8.4	1.5–3.8 mg/dl
Apolipoprotein C3	115.5	12.8	5.4–9.0 mg/dl
Apolipoprotein E	57.4	6.8	2.8–4.6 mg/dl
Apolipoprotein E phenotype	4/4		
LPL mass	207	ND	164–284 ng/ml
LPL activity	0.145	ND	0.166–0.226 μmol/ml min
HTGL activity	0.255	ND	0.158–0.530 μmol/ml min

ND: not determined.

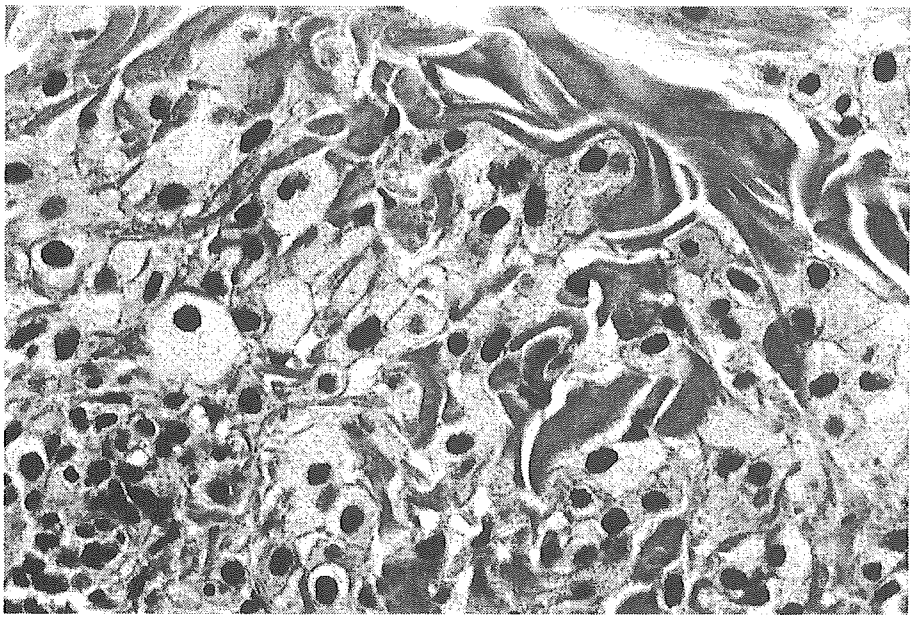

Fig. 2. Histopathology of the biopsy specimen of eruptive xanthoma (H&E staining, ×400 in original magnification). Multiple foamy histiocytes are seen throughout the dermis. A majority of these cells are mononuclear, and the Touton type giant cells are absent.

less than 200 mg/dl. Along with the improvement in glycemic control, serum levels of triglyceride and total cholesterol rapidly decreased without the administration of any hypolipidemic agents. Simultaneously, skin eruptions gradually disappeared at 1 month after the admission. On day 23, serum concentrations of chylomicrons; VLDL; apolipoprotein C2, C3, and E were restored to their normal reference ranges (Table 2), whereas the serum triglyceride and total cholesterol concentrations were 254 and 291 mg/dl, respectively. At the time of discharge (day 41), serum levels of triglyceride, total, and HDL cholesterol were 88, 169, and 31 mg/dl, respectively.

After the achievement of good glycemic control, an insulin-modified frequently sampled intravenous glucose tolerance test was performed as described

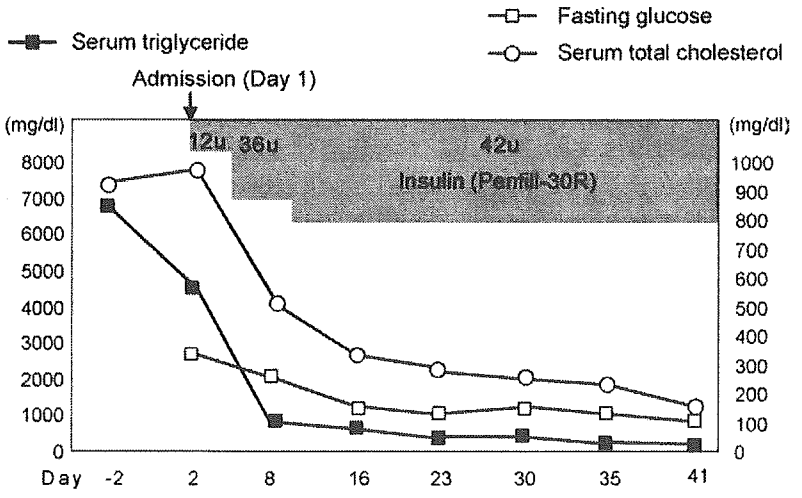

Fig. 3. The levels of fasting glucose, serum triglyceride, and total cholesterol of the patient during the study.

previously [4]. Acute insulin response to glucose within 10 min after the glucose bolus was markedly decreased, that is, 14.3 [(μU/ml) 10 min] in the patient, whereas it was 165 ± 51 [(μU/ml) 10 min, mean ± S.E.] in the control subjects [5]. Minimal model analysis of plasma glucose and insulin kinetics yielded a zero insulin sensitivity index, suggesting severe insulin resistance even after the correction of hyperglycemia [6]. Glucose effectiveness (0.0153/min), that is, effects of glucose per se to normalize its own concentration, was also moderately decreased as compared to that in the control subjects (0.0203 ± 0.0022/min) [5].

After obtaining the patient's written informed consent, 22 mutations in the LPL gene, which have been demonstrated in the Japanese population (W-14X, N43S, Int2 + 1G/A, Y61X, G105R, G154V, G188E, I194T, V200A, D204E, A221del, C239X, R243C, R243H, A261T, F270L, C278R, N291del, S323C, A334T, W382X, and Int8 + 2T/C) were screened by Invader assay at the BML laboratory (http://www.bml.co.jp/genome/invadertech.html). All the mutations were shown to be present in the normal homozygous states.

3. Discussion

The present case displayed typical eruptive xanthomas, proven by histopathological analysis, associated with type V hyperlipoproteinemia and diabetes mellitus. Since eruptive xanthomas subsided with the achievement of glycemic control by insulin administration, the hyperlipidemia present in the subject can be regarded as the so-called diabetic lipemia [7]. Regarding the etiology of diabetes mellitus, the possibility of Type 1 diabetes mellitus was unlikely because of a strong family history of diabetes, demonstration of moderately decreased insulin secretion by C-peptide measurement, and absence of autoantibodies related to Type 1 diabetes. Although the patient was not obese, the dose of insulin required to correct hyperglycemia was not moderate (0.88 unit/kg), and minimal model analysis of an intravenous glucose tolerance test revealed severe insulin resistance. There might be some possibility of the existence of maturity-onset diabetes of the young (MODY) in this family because of the clustering of diabetic subjects and younger age of onset of the disease in the proband. However, it appears unlikely that the proband may have any known MODY mutations because subjects with such MODY mutations usually have deficient insulin secretion, but not insulin resistance [8]. Finally, after considering the various factors, she was diagnosed as having Type 2 diabetes.

In the present case, although the exact pathogenesis of insulin resistance remains to be clarified, measurements of several adipocytokines revealed the presence of hypoadiponectinemia. Adiponectin, an adipose tissue-derived circulating protein, has insulin-sensitizing and anti-atherogenic properties [9]. Circulating concentrations of adiponectin are known to be decreased in obesity and Type 2 diabetes [10], and the decrease in adiponectin concentration is considered to be one of the pathogenic factors for insulin resistance in Type 2 diabetic patients [11]. Since this lean patient showed markedly decreased adiponectin levels as compared to more obese Type 2 diabetic females, hypoadiponectinemia is likely to play a role in the evolution of insulin resistance.

In the present case, the etiology of type V hyperlipoproteinemia appears to be multifactorial. First, the presence of marked hyperglycemia and ketosis, on admission, suggests deficient insulin action; this could be associated with a transient deficiency of LPL, a key enzyme of triglyceride catabolism, and increased lipolysis leading to VLDL overproduction [12]. This assumption is supported by the fact that the achievement of glycemic control by insulin therapy resulted in the normalization of hyperlipidemia. The decrease in insulin action can be due to defective insulin secretion, insulin resistance, or both. In the present case, minimal model analysis revealed a zero insulin sensitivity index [6] even after the hyperglycemia was corrected and glucose toxicity was removed. Therefore, the insulin resistance might have been much greater on admission and, presumably, might have contributed to the decreased insulin action to a great extent. Independent of the association with insulin resistance, hypoadiponectinemia has been recently shown to be directly associated with decreased post-heparin LPL activity [13]. Therefore, hypoadiponectinemia could also account for the decreased LPL activity as well as the pathogenesis of insulin resistance.

It is well recognized that the degree of hypertriglyceridemia is variable among diabetic subjects who have marked hyperglycemia. Therefore, some

Table 3
Eruptive xanthoma and diabetes mellitus (literature review)

Onset age of xanthoma (years)	Sex	Onset age of diabetes (years)	Type of diabetes	BMI (kg/m^2)	Family history of diabetes	Fasting glucose (mg/dl)	HbA_{1c} (%)	TG (mg/dl)	T-Chol (mg/dl)	Type of hyperlipidemia	Reference
20	Male	17	NR	NR	+	300	NR	1525	839	V	[23]
29	Male	27	2	31.1	+	365	NR	1129	596	IV	[24]
24	Male	21	2	34.3	+	200	NR	1969	535	V	[25]
19	Female	19	2	18.2	–	185	NR	1040	366	III	[26]
35	Male	25	2 (probable)	36.2	+	211	10.4	4188	888	V	[27]
30	Male	27	2 (probable)	28	+	349	NR	6640	780	V	[28]
35	Male	28	2 (probable)	34.6	–	261	8.6	3165	402	V	[29]
15	Female	13	2	32	+	283	15.5	6230	682	V	[30]
35	Male	34	2	27.1	+	245	NR	4300	1095	V	[31]
43	Male	43	2 (probable)	26.6	+	210	10.2	2008	655	V	[32]
45	Female	40	2	27.6	–	134	8.6	2572	558	IV	[33]
17	Female	13	2	NR	–	322	11	3275	465	I	[34]
43	Male	39	2	31.9	+	242	8.7	2901	402	V	[35]
40	Male	40	2	NR	+	398	NR	11700	1067	V	[36]
28	Female	15	2	27	+	171	11.5	2785	750	IV	[37]
38	Male	38	2	NR	NR	241	13.4	8869	1268	V	[38]
20	Female	20	2	18.9	+	350	15.7	6880	901	V	Present case

NR: not recorded.

genetic and environmental susceptibility to hypertriglyceridemia should also be considered [14]. The contribution of drugs, such as corticosteroids or estrogen, alcohol consumption, and hypothyroidism, to causing hypertriglyceridemia appear unlikely based on the history and laboratory findings. Apolipoprotein C2 deficiency, which can result in type V hyperlipoproteinemia, was not observed. Although compound heterozygous two mutations in the LPL gene were demonstrated in a subject with diabetic ketoacidosis and severe hypertriglyceridemia [15], the present case did not have any known LPL mutations, seen in the Japanese population, both in heterozygous and homozygous manners. However, the presence of very rare mutations cannot be completely ruled out at present.

The subject showed apolipoprotein E phenotype of E4/4; this phenotype is associated with an increased risk of coronary heart disease [16], vascular dementia [17], and late-onset familial Alzheimer disease [18]. With regard to its association with hyperlipidemia, Ghiselli et al. [19] first reported the increased prevalence of apolipoprotein E4 phenotype in type V hyperlipoproteinemia. According to their results, approximately one-third of the patients with type V hyperlipoproteinemia were homozygous for the E4 allele. Supporting this finding, apolipoprotein E4 gene frequency was also found to be increased in obese subjects with hypertriglyceridemia [20]. Increased intestinal cholesterol absorption [21] and/or postprandial hyperlipidemia [22] have been postulated to explain this association.

Table 3 summarizes the clinical characteristics of 17 subjects (11 males and 6 females, including the present case) who had diabetes mellitus and eruptive xanthoma; they were found by literature review [23–38]. With the exception of a few subjects, eruptive xanthomas were noted at the time of initial diagnosis of diabetes or within a few years of the diagnosis. Most subjects were diagnosed as having Type 2 diabetes, and the age of onset of diabetes was less than 40 years in 14 (82%) of the 17 subjects. Consistent with Type 2 diabetes, obesity with BMI greater than 25 kg/m^2 and positive family history of diabetes were present in most of the subjects. The levels of fasting glucose, HbA_{1c}, serum triglyceride, and total cholesterol were markedly elevated, and 12 subjects were diagnosed with type V hyperlipoproteinemia (71%). Obesity and poor glycemic control generally indicates the presence of insulin resistance, which results in decreased LPL activity and increased VLDL production. Elevated HbA_{1c} levels suggest that hyperglycemia may have persisted for at least 1 or 2 months, and eruptive xanthomas may develop during these periods with persistent hypertriglyceridemia. Among all the reviews, we did not observe any case report that described marked hypertriglyceridemia and eruptive xanthomas in Type 1 diabetic subjects. The duration of hypertriglyceridemia may not have been long enough for the development of eruptive xanthomas in case of severe insulin deficiency of Type 1 diabetes.

The present case showed a few Marfanoid features, such as arachnodactyly and elongated arm span; however, no abnormalities in the lens and cardiovascular system were observed, and none of the family members showed typical Marfanoid features. Therefore, at present, making a definite diagnosis of Marfan syndrome appeared to be difficult [39]. A case report of a female with Marfan syndrome and Type 1 diabetes has been described previously [40]; however, the relationship between Marfan syndrome and Type 2 diabetes remains unknown.

In conclusion, this paper has reported a case of a female patient with early onset Type 2 diabetes who displayed marked hyperglycemia, hypertriglyceridemia (type V hyperlipoproteinemia) and eruptive xanthomas. The patient was also characterized by Marfanoid appearance, presence of insulin resistance, and hypoadiponectinemia, despite the absence of obesity. It appeared unlikely that the LPL gene mutations contributed to hypertriglyceridemia. The clustering of apolipoprotein E4/4 and hypoadiponectinemia, in addition to insulin resistance and poor glycemic control, might have resulted in hypertriglyceridemia with eruptive xanthomatosis in this subject.

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Is the Diagnosis of Metabolic Syndrome Useful for Predicting Cardiovascular Disease in Asian Diabetic Patients?

Analysis from the Japan Diabetes Complications Study

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OBJECTIVE — The metabolic syndrome (MetS) is believed to be associated with an increased risk of cardiovascular disease (CVD). Although its prevalence is extremely high among diabetic patients, its prevalence in those with no history of CVD has not been determined. Moreover, prospective studies published on the association between MetS and cardiovascular events in diabetic populations have used only the World Health Organization (WHO) definition of MetS and included only white European subjects. The aim of this study was to determine the prevalence of MetS, as defined by both the WHO and the National Cholesterol Education Program (NCEP), and its predictive value for CVD in Asian diabetic patients in a long-term, prospective setting.

RESEARCH DESIGN AND METHODS — The baseline characteristics and incidence/hazard ratio of cardiovascular events (coronary heart disease and stroke) were determined in 1,424 Japanese type 2 diabetic patients with and without MetS, as defined by WHO (WHO-MetS) or the NCEP.

RESULTS — A high prevalence (38–53%, depending on sex and definition) of MetS was found among diabetic patients, even those with no history of CVD. During the 8-year study period, only WHO-MetS was a predictor for CVD in female patients. In male patients, although both definitions of MetS were significant predictors for CVD, individual components of MetS, such as hyperlipidemia or hypertension, were equivalent or better predictors.

CONCLUSIONS — We found that MetS is relatively common in diabetic patients with no history of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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The metabolic syndrome (MetS) is an important cluster of metabolic abnormalities linked with insulin resistance and cardiovascular disease (CVD) (1). The diagnostic criteria of MetS proposed by the World Health Organization (WHO-MetS) (2) and the National Cholesterol Education Program (NCEP-MetS) (3) are currently the most widely used. Although the prevalence of MetS in the general population reportedly differs widely among ethnic groups (4–8) and according to the definition of MetS used (7,9–11), the prevalence among patients with known diabetes is consistently high (70–90%) regardless of ethnicity or definition (12–20). Considering the high prevalence of CVD in the diabetic population (21) and the fact that subjects with a history of CVD often have multiple cardiovascular risk factors, it has been speculated that the extremely high prevalence of MetS among diabetic patients (12–20) may be due to the large number of patients who already have a history of CVD. However, the prevalence of MetS in diabetic patients without CVD has not been widely investigated to date. It is rational to examine this because diabetic patients with MetS have a higher incidence of CVD than those without MetS (15,16) and MetS is a stronger risk factor for CVD in patients with type 2 diabetes than in nondiabetic subjects (12).

Most prospective studies have shown that subjects with MetS are at increased risk of incident CVD (22,23) and mortality due to CVD (9,24–27). However,

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; HOMA-IR, homeostasis model assessment of insulin resistance; JDCS, Japan Diabetes Complications Study; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization; WHR, waist-to-hip ratio.

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

many of these studies excluded diabetic patients from their study populations (9,22–24). Diabetic patients are known to be at greater risk for CVD than nondiabetic subjects (21), and it has been suggested that MetS is responsible for the increased prevalence of coronary heart disease (CHD) seen in diabetic patients (20). Therefore, it is important to evaluate the predictive value of MetS on incident CVD in diabetic patients in long-term, prospective studies. To the best of our knowledge, there have been four cohort studies specifically targeting diabetic patients to determine the relative risk of MetS on the incidence of CVD (12,15,16) and mortality due to CVD (17). Although these studies involved only white European subjects and used only the WHO definition of MetS, most of them (12,15,16) demonstrated, as expected, that the presence of MetS is associated with at least a severalfold increase in the risk of CVD. The above findings notwithstanding, it remains unclear 1) whether such predictive values of MetS are also applicable to diabetic patients of other ethnicities, 2) which features of MetS are the best predictors of CVD and should become the critical therapeutic targets for the optimal management of CVD risk in diabetic patients (28), and 3) whether the commonly used NCEP definition of MetS (3) possesses the same predictive value for CVD as the WHO definition in diabetic patients.

The incidence of CVD in Asian subjects is known to be much less than in white subjects in general (29) and in diabetic populations in particular (30). In addition, the degree of obesity is very different between white and Asian diabetic patients (31,32), and the impact of obesity on CHD risk is known to be entirely different between whites and Asians (33,34). These differences could affect the apparent clinical significance of MetS (35,36), so that it is questionable whether the overall concept of MetS itself and the diagnosis of MetS under the present definitions based on data from mostly European and American patients are applicable to the evaluation of CVD risk in Asian diabetic patients. Therefore, in this long-term, prospective study of Japanese diabetic patients with no history of CVD, we determined the prevalence of MetS and analyzed its individual features and predictive value for incident CVD using the two most widely used definitions of MetS (2,3). Such comparisons are helpful in possibly establishing a global definition of MetS (10,37) and are also warranted to determine if there is heterogeneity in the power of individual MetS components to predict CVD (28).

RESEARCH DESIGN AND METHODS

— The Japan Diabetes Complications Study (JDCS) is a nationwide, multicenter, prospective study of type 2 diabetic patients (38). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels >6.5% were recruited and registered. The eligibility criteria for participating patients has been previously described (38). The duration of the study was 8 years. Of the 2,205 patients, the present study focused on 1,424 patients (771 men and 653 women) who had a complete set of data, including those parameters necessary to satisfy the WHO (2) and NCEP (3) criteria for the definition of MetS at baseline. The JDCS protocol, which is in accordance with the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutes and was undertaken in accordance with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare. All of the study participants gave written informed consent.

Both the WHO (2) and the NCEP (3) definitions were used to diagnose MetS in this study. However, because the original cut-off for abdominal obesity in the NCEP definition (waist circumference ≥102 cm for men and ≥89 cm for women) has previously been shown to be inappropriate for Asian populations (35,37) and the number of subjects who met these criteria was extremely low, the cut-off limit was adjusted according to the criteria proposed by the Japan Society for the Study of Obesity (≥85 cm for men or ≥90 cm for women), which were based on the risk of obesity-related disorders in a Japanese population (39). The WHO criteria for obesity were adopted because the waist-to-hip ratio (WHR) was used rather than waist circumference. The criteria used for analysis in this study are shown in Table 3. Because all of the study subjects were diabetic, those who fulfilled two or more of criteria 1a, 2a, 5, or 6 were classified as having WHO-MetS and those who fulfilled two or more of criteria 1b, 2b, 3, or 4 were diagnosed as having NCEP-MetS, using a modified NCEP definition (Table 3). For comparisons with other traditional risk factors for CVD, we also evaluated high LDL cholesterol levels, cigarette smoking, and excessive alcohol intake (40). Medication use, including agents for hypertension and hyperlipidemia, were not considered when diagnosing MetS in this study.

Waist and hip circumferences were measured at the umbilicus and trochanter level, respectively. A baseline dietary survey, comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information regarding cigarette smoking was collected using a standardized questionnaire. All laboratory tests were undertaken using the standard methods of each of the participating institutes, apart from the HbA_{1c} assays, which used a common standard, with 5.8% as the upper normal limit. Plasma LDL cholesterol was calculated using Friedewald's equation, except for triglyceride levels >400 mg/dl, in which case the LDL cholesterol data were treated as "missing." To estimate insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was used (41). Plasma insulin levels and the HOMA-IR were not evaluated in patients treated with insulin.

Patients were assessed for CHD and stroke at baseline and yearly thereafter. In all subjects, a 12-lead electrocardiogram (ECG) was recorded at each assessment. Fatal and nonfatal CHD and stroke events identified during follow-up were certified by at least two members of the experts' committee who were masked as to risk factor status and the other member's diagnosis. With regard to CHD, myocardial infarction was defined according to the WHO Monitoring of Trends and Determinants in Cardiovascular Disease criteria (42) and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by using nitroglycerine, as validated by exercise-positive ECG and/or angiography. Stroke events were defined as a constellation of focal or global neurological deficits of sudden or rapid onset and for which there was no apparent cause other than a vascular accident, as determined by a detailed history, a neurological examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were

classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (43). No cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were included. Only "first-ever" CHD or stroke events during the study period were counted for the analysis; if a patient had both CHD and stroke events, each event was counted separately.

Data are presented as means ± SD or as a proportion, unless otherwise specified. To compare the distributions of baseline characteristics between groups, Wilcoxon's rank-sum test or Fisher's exact test was used. Incidence rates in the two groups were assessed by a score test under the Poisson assumption. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI) of MetS risk factors with CHD, stroke, or both. Statistical analyses were performed separately by sex. The SAS software package (Version 8.0, Cary, NC) was used for all analyses. $P < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics and prevalence of the metabolic syndrome

The baseline characteristics of the study subjects are shown in Table 1. In all, 51% of male and 53% of female subjects met WHO criteria for MetS, whereas 45% of male and 38% of female subjects met NCEP criteria for MetS. Plasma insulin levels and HOMA-IR were significantly higher in patients with MetS (both definitions) than in those without MetS; however, there were no significant differences in HbA_{1c} or the frequency of oral hypoglycemic agent use. Insulin usage was significantly lower in women with MetS by either definition and in men with NCEP-MetS. Blood pressure and serum triglycerides were significantly higher and HDL cholesterol was significantly lower in MetS patients, despite the fact that the use of medications for both hypertension and hyperlipidemia was much more common than in patients without MetS. Daily energy intake did not differ between patients with and without MetS (data not shown).

Incidence of cardiovascular disease during follow-up

During the 8-year study period, the total number of CVD events was 117, comprised of 62 CHD and 59 stroke events. The combined incidence (per 1,000 patient-years) of CHD and/or stroke was significantly greater in patients with MetS (except in female patients with NCEP-MetS) than in those without MetS (Table 2).

Hazard ratios of the metabolic syndrome and its individual components for coronary heart disease and stroke

HRs were calculated to determine which definition of MetS was the better predictor of CVD and which of the individual MetS components (or other classic risk factors) could most efficiently predict CVD events in our subjects (Table 3). In male patients, WHO-MetS was not significantly associated with an increased risk for either CHD or stroke separately, but was associated with the combination of both (HR = 1.6). Triglyceride, LDL cholesterol (both for CHD), and blood pressure (≥140/90 mmHg) levels (for stroke) showed higher HRs. NCEP-MetS was a significant predictor of CHD in male patients, although its HR (1.9) was lower than that for triglycerides (2.9) or LDL cholesterol (2.1). Thus, neither definition of MetS was a substantially better predictor of CVD than the component parts in male patients. In contrast, in the female patients, WHO-MetS was a significant and strong predictor of CHD (HR = 2.8), stroke (HR = 3.7), and both CHD and stroke (HR = 3.2). In female patients, none of the individual elements nor the other classic risk factors showed significant increases in HRs, with the exception of hypertension (≥140/90 mmHg) for stroke, although its HR (2.4) was still lower than that for WHO-MetS. NCEP-MetS was not a significant risk factor for CHD or stroke in female patients (Table 3).

To examine the clustering effects of the individual components of MetS, the association between CVD risk and the number of MetS components fulfilled (other than diabetes) was analyzed (Table 3). Increasing the cut-off component number for the diagnosis of NCEP-MetS from ≥2 to ≥3 in male subjects did not dramatically improve the HR but did greatly reduce the number of patients diagnosed as having MetS, from 45 to 14.5% (Table 3). In female patients, changing the diagnostic cut-off component numbers was not particularly beneficial in improving the prognostic value of WHO-MetS (Table 3).

CONCLUSIONS — The prevalence of MetS in our diabetic patients who were free from CVD was not as high as that reported in previous studies that included patients with previous CVD (12–20) but was nevertheless relatively high (38–53%). Although we did not have age-matched nondiabetic control subjects, the prevalence of MetS was much higher than that reported in Japanese general population workers, namely 19.5% in men and 7.9% in women (33). Hypertension and dyslipidemia are much more common in diabetic patients than in nondiabetic subjects (21), and it has been speculated that the features of MetS more easily aggregate, even in the absence of current or previous CVD, leading to the observed increase in the prevalence of MetS. On the other hand, the prevalence of NCEP-MetS in the U.S. general population age 50 years and older is 44% (20), which is relatively close to that in our Japanese diabetic patients. However, even in the U.S. (excluding Asian Americans), the prevalence of MetS in those who have a BMI range equivalent to that of Japanese subjects is not >10% (44). This implies that in the U.S., obesity has a potent impact on the prevalence of MetS, as has also been shown in a recent study (45). This is in contrast to findings in Japan, where diabetes rather than obesity may have the greater influence on the prevalence of MetS, as Japanese diabetic patients are not obese by comparison with white diabetic patients or nondiabetic Japanese subjects (31,32).

The clinical importance of MetS is related to its putative impact on CVD morbidity and mortality. Among Italian patients with type 2 diabetes, the risk for CVD was 4.9 (CI 1.2–20.7) times higher in patients with WHO-MetS than in those without it (16), which was a higher rate than that seen in our male (1.6 [CI 1.0–2.6] times) and female (3.2 [CI 1.6–6.5] times) patients. These results suggest that the clinical impact of MetS on diabetic patients varies by ethnic group. Comparing cardiovascular risk factors in our Japanese patients to those in patients in the U.K. Prospective Diabetes Study (UKPDS) (46,47), hypertension is a common

Table 1—*Baseline characteristics of study subjects, grouped by metabolic syndrome status*

	Total	WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
		Without	With	*P*	Without	With	*P*
n							
Men	771	376 (48.8)	395 (51.2)	—	424 (55.0)	347 (45.0)	—
Women	653	310 (47.4)	343 (52.6)	—	405 (62.0)	248 (38.0)	—
Age (years)							
Men	58.2 ± 7.4	57.4 ± 7.6	58.9 ± 7.2	0.01	58.0 ± 7.6	58.4 ± 7.2	0.50
Women	58.7 ± 7.4	57.9 ± 7.7	59.5 ± 7.0	0.01	58.4 ± 7.4	59.4 ± 7.2	0.11
Diabetes duration (years)							
Men	10.9 ± 7.6	11.0 ± 7.6	10.9 ± 7.6	0.66	11.5 ± 7.8	10.2 ± 7.4	0.01
Women	10.1 ± 6.7	10.7 ± 7.3	9.5 ± 6.0	0.10	10.6 ± 7.0	9.4 ± 6.0	0.07
BMI (kg/m^2)							
Men	22.9 ± 2.6	22.0 ± 2.4	23.7 ± 2.6	<0.01	21.8 ± 2.3	24.2 ± 2.4	<0.01
Women	23.4 ± 3.3	22.3 ± 3.0	24.3 ± 3.3	<0.01	22.6 ± 3.1	24.6 ± 3.3	<0.01
Waist circumference (cm)							
Men	82.3 ± 7.7	79.0 ± 7.1	85.3 ± 7.0	<0.01	78.4 ± 6.4	87.0 ± 6.5	<0.01
Women	76.5 ± 9.8	72.4 ± 8.3	80.1 ± 9.7	<0.01	74.1 ± 8.6	80.4 ± 10.4	<0.01
Waist-to-hip ratio							
Men	0.89 ± 0.07	0.86 ± 0.05	0.92 ± 0.06	<0.01	0.87 ± 0.06	0.92 ± 0.06	<0.01
Women	0.83 ± 0.08	0.80 ± 0.06	0.86 ± 0.07	<0.01	0.82 ± 0.07	0.86 ± 0.08	<0.01
Blood pressure (mmHg)							
Men	132 ± 16/78 ± 10	124 ± 13/74 ± 9	139 ± 15/81 ± 10	<0.01	127 ± 16/75 ± 9	137 ± 15/81 ± 9	<0.01
Women	132 ± 17/76 ± 10	124 ± 13/73 ± 9	139 ± 16/79 ± 11	<0.01	128 ± 17/74 ± 10	138 ± 14/80 ± 10	<0.01
HbA_{1c} (%)							
Men	7.61 ± 1.36	7.53 ± 1.42	7.67 ± 1.30	0.05	7.54 ± 1.36	7.68 ± 1.36	0.18
Women	8.05 ± 1.45	8.07 ± 1.51	8.04 ± 1.40	0.79	8.09 ± 1.47	7.99 ± 1.42	0.41
Fasting plasma glucose (mmol/l)*							
Men	8.3 (7.2–10.0)	8.2 (7.0–9.7)	8.6 (7.4–10.4)	<0.01	8.2 (7.1–9.8)	8.6 (7.4–10.3)	0.02
Women	8.6 (7.3–10.2)	8.6 (7.2–10.2)	8.6 (7.3–10.2)	0.74	8.6 (7.2–10.3)	8.5 (7.4–9.9)	0.77
Fasting plasma insulin (pmol/l)†‡							
Men	6.2 (0.5–1.9)	5.4 (0.5–1.9)	7.2 (0.5–1.9)	<0.01	5.2 (0.5–1.9)	7.7 (0.5–1.9)	<0.01
Women	7.1 (0.5–1.9)	5.9 (0.5–1.9)	8.3 (0.6–1.8)	<0.01	6.2 (0.5–1.9)	8.7 (0.5–1.9)	<0.01
HOMA-IR‡							
Men	3.1 ± 3.1	2.6 ± 2.6	3.6 ± 3.4	<0.01	2.4 ± 2.1	3.9 ± 3.8	<0.01
Women	3.3 ± 2.6	2.8 ± 2.2	3.8 ± 2.8	<0.01	2.9 ± 2.1	4.1 ± 3.1	<0.01
Serum total cholesterol (mmol/l)							
Men	5.01 ± 0.90	4.93 ± 0.84	5.09 ± 0.94	0.01	4.97 ± 0.82	5.07 ± 0.98	0.16
Women	5.44 ± 0.85	5.38 ± 0.84	5.50 ± 0.86	0.05	5.41 ± 0.83	5.50 ± 0.89	0.28
Serum HDL cholesterol (mmol/l)							
Men	1.34 ± 0.39	1.42 ± 0.39	1.27 ± 0.38	<0.01	1.48 ± 0.38	1.18 ± 0.34	<0.01
Women	1.47 ± 0.44	1.57 ± 0.45	1.37 ± 0.41	<0.01	1.65 ± 0.43	1.17 ± 0.26	<0.01
Serum triglycerides (mmol/l)†							
Men	1.2 (0.6–1.6)	1.0 (0.7–1.5)	1.5 (0.6–1.6)	<0.01	1.0 (0.7–1.5)	1.6 (0.6–1.6)	<0.01
Women	1.1 (0.6–1.7)	0.9 (0.6–1.6)	1.4 (0.6–1.6)	<0.01	9 (0.7–1.5)	1.6 (0.6–1.6)	<0.01

Current smoker (%; men/women)	43.9/8.7	46.6/8.1	41.3/9.2	0.08/0.38	44.7/7.1	42.9/11.3	0.33/0.049
Excessive alcohol intake (%; men/women)§	12.4/0.2	8.2/0.0	16.4/0.3	<0.01/0.51	7.7/0.3	18.4/0.0	<0.01/0.62
OHA use (without insulin) (%; men/women)	72/77	72/76	73/78	0.38/0.33	72/75	72/79	0.50/0.20
Insulin use (with or without OHA) (%; men/women)	16/20	18/24	15/16	0.16/0.01	20/22	11/15	<0.01/0.02
Medication for hypertension (%; men/women)	22/29	12/17	32/40	<0.01/<0.01	16/23	30/40	<0.01/<0.01
Medication for hyperlipidemia (%; men/women)	15/35	11/30	19/39	<0.01/<0.01	10/32	21/40	<0.01/0.02

Data are *n* (%), means ± SD, *median (interquartile range), or †geometric means (1 SD). ‡Patients with insulin therapy were excluded. §Excessive alcohol intake was defined as more than three drinks (38 g ethanol) per day. OHA, oral hypoglycemic agent.

and potent risk factor for stroke (Table 3) (46). By contrast, HDL cholesterol levels, hypertension, and smoking, all of which were identified as significant risk factors for CHD in UKPDS patients (47), were not associated with a significant elevation of HRs in our Japanese patients (Table 3). Instead, triglyceride levels, which were not significant in UKPDS patients (47), were a strong predictor for CHD in male Japanese patients. These findings imply that the critical therapeutic targets among the components of MetS for preventing cardiovascular complications (28) may need to be modified according to a patient's ethnic group.

Most of the previous studies evaluating the predictive power of MetS for CVD calculated the HRs by including sex as one of the independent variables for statistical adjustment, and very few studies have analyzed CVD risk separately by sex (24). Sex is reportedly an independent predictor for CVD, with an odds ratio of 2.6, which is larger than that of age, HbA_{1c}, and even of MetS itself in type 2 diabetic patients (16). Our results revealed drastic differences in the HRs between sexes. In our female patients, WHO-MetS presented an increased risk for CVD events to a greater degree than could be predicted by the sum of the individual components (Table 3), whereas, in contrast, in our male patients, WHO-MetS was not even a significant risk factor for CVD. At baseline, obvious sex differences were observable in the proportion of subjects who smoked or consumed excessive alcohol, both of which were much higher in male patients. Of particular interest, the proportion of male subjects with excessive alcohol intake was at least twice as high in male patients with MetS than in those without MetS, whereas the proportion of current smokers did not differ in patients with and without MetS (Table 1). It can be speculated that excessive alcohol intake could be closely associated with MetS in male Japanese diabetic patients. Moreover, moderate alcohol intake, which has been shown to be beneficial for preventing CHD in U.S. and European diabetic patients, is not beneficial for Japanese patients (40).

Few studies have applied both the WHO and NCEP definitions of MetS to the same subjects to compare the prevalence of MetS or its predictive value for CVD. It has been reported that the prevalence of WHO-MetS is generally higher than that of NCEP-MetS in both sexes (7,12). This was confirmed in our Japanese diabetic subjects, although the difference in prevalence was not great. Regarding the predictive value of MetS, in subjects without diabetes or other cardiovascular risks, Hunt et al. (27) reported that the NCEP-MetS tended to be more predictive for cardiovascular mortality than the WHO-MetS, whereas Lakka et al. (9) reported a contrary result. In our diabetic patients, the NCEP guidelines, even modified for optimal use by Japanese subjects, were not more predictive than the WHO guidelines in female patients nor did they show excellent clinical usefulness in male patients. One possible explanation for this difference in our patients could be the hypertension cut-off used, with 140/90 mmHg in the WHO defini-

Table 2—*Incidence of coronary heart disease and/or stroke (per 1,000 patient-years) among study subjects grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total (%)	Without (%)	With (%)	*P*	Without (%)	With (%)	*P*
Incidence among Men							
CHD	9.8	8.4	11.3	0.34	7.0	13.5	0.04
Stroke	7.7	5.1	10.3	0.05	6.6	9.1	0.35
CHD and/or stroke	17.1	12.7	21.6	0.03	13.0	22.6	0.02
Incidence among Women							
CHD	5.5	2.9	8.0	0.04	4.4	7.3	0.27
Stroke	7.2	2.8	11.2	<0.01	6.2	8.8	0.38
CHD and/or stroke	12.6	5.7	19.0	<0.01	10.7	15.6	0.22

Table 3—*Patient prevalence at baseline and hazard ratios for coronary heart disease, stroke, or both in Japanese study subjects grouped by metabolic syndrome status*

	Prevalence at baseline		Hazard ratios for CHD		Hazard ratios for stroke		Hazard ratios for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
Criteria of individual components								
1a. BMI >30 or WHR >0.90 (men) or >0.85 (women)	39.4	37.5	1.3 (0.7–2.5)	1.2 (0.5–3.0)	1.3 (0.7–2.6)	1.1 (0.5–2.3)	1.4 (0.8–2.2)	1.2 (0.6–2.1)
1b. Waist circumference ≥85cm (men) or ≥90 cm (women)	36.7	9.6	1.7 (0.9–3.0)	1.0 (0.2–4.4)	0.90 (0.4–1.9)	1.1 (0.3–3.7)	1.3 (0.8–2.1)	1.1 (0.4–2.8)
2a. SBP ≥140 or DBP ≥90 mmHg	38.9	38.9	0.8 (0.4–1.6)	1.0 (0.4–2.6)	2.1 (1.1–4.3)	2.4 (1.1–5.5)	1.3 (0.8–2.1)	1.8 (1.0–3.2)
2b. SBP ≥130 or DBP ≥85 mmHg	60.7	62.2	0.9 (0.5–1.6)	0.9 (0.4–2.2)	1.4 (0.7–2.9)	1.8 (0.7–4.5)	1.1 (0.6–1.7)	1.2 (0.7–2.4)
3. Triglycerides ≥150 mg/dl	24.8	21.0	2.9 (1.6–5.3)	1.7 (0.6–4.4)	1.1 (0.5–2.4)	0.7 (0.2–1.9)	2.0 (1.2–3.2)	1.1 (0.5–2.2)
4. HDL cholesterol ≤40 mg/dl	19.3	36.3	1.8 (0.9–3.5)	1.5 (0.6–3.6)	1.0 (0.4–2.5)	1.3 (0.6–2.9)	1.6 (0.9–2.6)	1.3 (0.7–2.4)
5. Triglycerides ≥150 mg/dl or HDL cholesterol <35 mg/dl	28.5	27.0	2.8 (1.6–5.2)	1.8 (0.7–4.5)	0.9 (0.4–1.9)	1.6 (0.7–3.5)	1.8 (1.1–2.9)	1.6 (0.9–2.9)
6. Urinary albumin excretion >30 μg/g creatinine	51.2	57.7	1.2 (0.6–2.3)	2.9 (0.9–8.7)	1.8 (0.9–3.8)	1.1 (0.5–2.4)	1.4 (0.9–2.3)	1.6 (0.8–3.0)
7. LDL cholesterol ≥120 mg/dl	45.1	65.2	2.1 (1.1–3.9)	1.2 (0.5–3.2)	0.9 (0.5–1.8)	0.6 (0.3–1.3)	1.4 (0.9–2.3)	0.8 (0.4–1.4)
8. Current smoker	43.9	8.7	1.4 (0.7–2.5)	0.6 (0.1–4.3)	0.9 (0.4–1.8)	2.5 (0.8–7.3)	1.2 (0.7–1.9)	1.6 (0.6–4.1)
9. Alcohol intake >3 drinks/day*	12.4	0.2	0.7 (0.3–2.1)	0.0 (0.0–0.0)	1.0 (0.4–2.8)	0.0 (0.0–0.0)	0.9 (0.4–1.8)	0.0 (0.0–0.0)
Number of components comprising WHO-MetS other than diabetes (i.e., among 1a, 2a, 5, and 6)								
0	18.6	16.4	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	81.5	83.6	1.7 (0.7–4.5)	3.9 (0.5–28.4)	1.0 (0.4–2.5)	2.3 (0.5–9.7)	1.2 (0.7–2.4)	2.8 (0.9–9.0)
≥2 (vs. <2; i.e., WHO-MetS)	51.2	52.5	1.3 (0.7–2.4)	2.8 (1.0–7.9)	2.0 (0.9–4.1)	3.7 (1.4–9.9)	1.6 (1.0–2.6)	3.2 (1.6–6.5)
≥3 (vs. <3)	21.8	20.7	1.8 (0.9–3.5)	1.3 (0.5–3.7)	2.1 (1.0–4.4)	1.1 (0.4–2.7)	1.9 (1.2–3.2)	1.2 (0.6–2.4)
Number of components comprising NCEP-MetS other than diabetes (i.e. among 1b, 2b, 3, and 4)								
0	20.1	21.6	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	79.9	78.4	1.9 (0.7–4.9)	1.6 (0.4–5.6)	1.0 (0.4–2.2)	6.4 (0.9–46.7)	1.3 (0.7–2.4)	2.7 (0.9–7.7)
≥2 (vs. <2; i.e., NCEP-MetS)	45.0	38.0	1.9 (1.0–3.6)	1.7 (0.7–4.0)	1.4 (0.7–2.8)	1.3 (0.6–2.8)	1.8 (1.1–2.8)	1.4 (0.8–2.5)
≥3 (vs. <3)	14.5	11.5	2.5 (1.3–4.9)	0.9 (0.2–3.7)	0.9 (0.3–2.4)	0.3 (0.0–2.2)	1.8 (1.0–3.2)	0.5 (0.2–1.7)

Data are percent or hazard ratios (95% CIs) and are grouped according to individual and combined cardiovascular risk factors mostly comprising the metabolic syndrome as defined by the World Health Organization or the National Cholesterol Education Program. *Equivalent to 38 g ethanol/day. DBP, diastolic blood pressure; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

tion being a significant predictor for stroke, whereas 130/85 mmHg in the NCEP definition is not.

The strengths of our study were that *1*) it is the first prospective study to determine the predictive value of MetS on CVD in Asian subjects, 2) the two most widely used definitions of MetS were applied to the same cohort for the evaluation of their clinical usefulness, and 3) the follow-up was mainly carried out in university or large general hospitals, which facilitated the reliable assessment of follow-up data and event diagnosis/records. Nevertheless, we acknowledge that the study had certain limitations: *1*) Our study subjects were hospital-based patients with diabetes of a relatively long duration; therefore, we cannot make inferences beyond a similar group. 2) We analyzed both intervention (lifestyle modification through diabetes self-management care) and control (continuance of conventional care) groups of the JDCS together, although mild intervention produced only limited differences in glycemic control (0.1–0.2% in HbA_{1c}) as well as a lack of significant differences in known classical cardiovascular risk factors, as previously reported (38). 3) We did not consider medication use in the diagnosis of MetS in this study. 4) Mortality was not analyzed because we did not have sufficient occurrences at this stage of the study.

In conclusion, we found a high prevalence of MetS among diabetic patients with no history of CVD. For Japanese female patients with type 2 diabetes, WHO-MetS but not NCEP-MetS was predictive for CVD. In male patients, although both WHO-MetS and NCEP-MetS were somewhat predictive for CVD, hyperlipidemia or hypertension had equivalent or higher HRs for CVD and seemed to be sufficient for the prediction of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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APPENDIX

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