Original Article

Components of Metabolic Syndrome and their Combinations as Predictors of Cardiovascular Disease in Japanese Patients with Type 2 Diabetes. Implications for Improved Definition. Analysis from Japan Diabetes Complications Study (JDCS)

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***Aim*: The prognostic power of metabolic syndrome (MetS) in patients with diabetes has been studied with inconsistent results depending on the definition of MetS. To clarify the best combination of MetS components to predict future cardiovascular disease (CVD) events, we estimated CVD risk in Japanese patients with type 2 diabetes according to MetS components.**

***Methods*: Patients were categorized according to the presence three MetS components in addition to hyperglycemia. hypertension, dyslipidemia and excess waist circumference (WC) (according to either Japanese or Asian cut-off values). Hazard ratios for CVD events were compared in patients with various categories of MetS components.**

***Results*: At least two components of MetS were required for a significantly elevated risk for CVD; however, component combinations with significantly increased risk differed depending on gender or the WC cut-off value. Any two among 1) excess WC (men ≥90 cm, women ≥80 cm); 2) hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of an antihypertensive agent); and 3) dyslipidemia (triglycerides ≥150 mg/dL or HDL-cholesterol <40 mg/dL or use of drug treatment) could be used to identify significantly higher risk (approximately twice) for CVD regardless of gender.**

***Conclusions*: The results suggest that the current MetS criteria should be modified when applied to patients with type 2 diabetes.**

J Atheroscler Thromb, 2009; 16:380-387.

Key words; Diabetic macroangiopathy, Cardiovascular risk factors, Hypertension, Dyslipidemia

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Received: August 6, 2008
Accepted for publication: January 20, 2009

Introduction

Patients with diabetes are at greater risk for cardiovascular disease (CVD) than non-diabetic subjects, and metabolic syndrome (MetS), a constellation of multiple cardiometabolic risk factors, is strongly asso-

ciated with increased risk of CVD events; however, previously, we found that the diagnosis of MetS had only a limited prognostic value for future CVD events in Japanese patients with type 2 diabetes[1-3]. Since that time many reports have also addressed the issue of whether a diagnosis of MetS is predictive in patients with diabetes, reflecting the need to identify diabetic patients at very high risk for CVD events in clinical settings; unfortunately, the results have been inconsistent[4-13]. Some studies[5-7, 10] revealed that the clinical relevance of a diagnosis of MetS as a predictor of CVD morbidity and mortality differs markedly among diabetic patients, depending on the definition of MetS. Moreover, the contribution of each MetS component to cardiovascular risk was shown to significantly vary in the general population[14].

These findings strongly suggest that various combinations of individual components of MetS could have substantially different contributions to CVD risk in diabetic patients. In fact, a recent cross-sectional study of 4020 German patients with type 2 diabetes[15] demonstrated considerably diverse odds ratios for established CVD according to heterogeneous clusters of traits; however, prospective studies evaluating the impact of specific combinations of MetS components on CVD risk in diabetic populations are scarce, although such a study in the general population has been published recently[16]. Such information would be useful for screening patients at extremely high risk of CVD as well as for improving the definition of MetS for a diabetic subgroup. For this purpose, we determined the prevalence of various combinations of MetS components among Japanese patients with type 2 diabetes and estimated the risks of CVD presented by these components in this patient group.

Methods

The Japan Diabetes Complications Study (JDCS) is a nationwide multi-center prospective study of type 2 diabetic patients[17]. In 1996, 2205 patients aged 40–70 years with previously diagnosed type 2 diabetes but no CVD were registered. The detailed protocol of the JDCS has been described previously[17]. Of the 2205 patients, 1424 (771 men and 653 women, mean age; 58.4±7.4 years) with a complete set of data, including the parameters necessary to satisfy the World Health Organization (WHO)[18] and the National Cholesterol Education Program (NCEP) Adult Treatment Panel Ⅲ (ATPⅢ)[19] criteria for the definition of MetS at baseline, were prospectively followed for 8 years for fatal/non-fatal coronary heart disease (CHD) and stroke events. CHD events consisted of angina pectoris and fatal/non-fatal acute myocardial infarction. A detailed definition of CHD and stroke events was previously described[1]. CHD and stroke events (hereafter referred to as CVD) identified during follow-up were confirmed by at least two members of the experts committee who were blinded as to risk factor status and the other member's diagnosis. The JDCS protocol was conducted according to the Declaration of Helsinki and received approval from the institutional review board. All participants gave written informed consent.

Thresholds for individual risk factors were adopted from the Japanese definition of MetS[20], which is similar to that of IDF[21] with the exception that hypertriglyceridemia and low HDL-cholesterolemia are combined as one component, i.e, 'dyslipidemia'. Since all subjects in this study had diabetes mellitus, 3 criteria other than an elevated fasting plasma glucose level (>110 mg/dL) were used: (i) excess WC (male ≥85 cm, female ≥90 cm), (ii) hypertension (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), and (iii) dyslipidemia (triglyceride >150 mg/dL and/or HDL-cholesterol <40 mg/dL). MetS is defined as the presence of excess WC and two of the following three parameters: hypertension, dyslipidemia and elevated fasting plasma glucose[20]. Subjects using agents for hypertension or hyperlipidemia were considered to have either hypertension or hyperlipidemia according to the recent MetS criteria[19, 21]. The alternative WC cut-off values for general Asians, as decided by the WHO and the International Diabetes Federation (IDF) definition (male ≥90 cm, female ≥80 cm)[19, 21], were used for additional evaluation.

Data are presented as the means±SD or as a proportion unless otherwise specified. WC in each group was assessed by Wilcoxon's rank sum test. Cox regression analysis was used to calculate the age-adjusted hazard ratio and 95% confidence intervals (CI) of risk factors for CVD. The SAS software package (Version 9.0, Cary, NC) was used for all analyses. $P<0.05$ was considered significant.

Results

Distribution of Patients According to Status of Risk Factor Clustering

Baseline characteristics of the study patients are shown in **Table 1**. Distribution of patients categorized by risk factor status employing either the Japanese or Asian WC cut-off is shown in **Fig. 1**. Approximately 60–70%, 30–0% or 20–25% of all diabetic patients, including both males and females, had hypertension,

Table 1. Baseline characteristics of patients analyzed

	Men	Women
Number of Patients (%)	771	653
Age (y)	58.2 ± 7.4	58.7 ± 7.4
Diabetes duration (y)	10.9 ± 7.6	10.1 ± 6.7
BMI (kg/m^2)	22.9 ± 2.6	23.4 ± 3.3
Waist circumference (cm)	82.3 ± 7.7	76.5 ± 9.8
Waist/Hip ratio	0.89 ± 0.07	0.83 ± 0.08
Blood pressure (mmHg)	132 ± 16/78 ± 10	132 ± 17/76 ± 10
HbA$_{1C}$ (%)	7.61 ± 1.36	8.05 ± 1.45
Fasting plasma glucose* (mmol/L)	8.3 (7.2, 10.0)	8.6 (7.3, 10.2)
Fasting plasma insulin* (pmol/L)#	6.2 (0.5, 1.9)	7.1 (0.5, 1.9)
Serum LDL cholesterol (mmol/L)	3.03 ± 0.86	3.38 ± 0.82
Serum HDL cholesterol (mmol/L)	1.34 ± 0.39	1.47 ± 0.44
Serum triglycerides** (mmol/L)	1.39 (0.75)	1.29 (0.72)
Current smoker (%)	43.9	8.7
OHA (without insulin) use (%)	72	77
Insulin (with or without OHA) use (%)	16	20
Medication for hypertension (%)	22	29
Medication for hyperlipidemia (%)	15	35

mean ± SD, *median (IQR) or **geometric mean (1SD), #patients on insulin therapy were excluded
OHA, oral hypoglycemic reagents

dyslipidemia or both, respectively. When the Japanese WC cut-off value (male ≥ 85 cm, female ≥ 90 cm) was applied, the proportion of female patients with excess WC was much lower than that of male patients. Among all diabetic patients, the proportion of patients having all 3 risk factors (i.e. excess WC, hypertension and dyslipidemia) was 13% among men but only 3% among women. When the Asian WC cut-off value (male ≥ 90 cm, female ≥ 80 cm) was used instead of the Japanese cut-off value, the proportion of female patients with excess WC increased nearly 4 times (approx. from 10 to 37%) while the proportion of male patients decreased by half (approx. from 37 to 18%).

CVD Risk of Patients in Individual and Combined Risk Category

Table 2 shows hazard ratios for CVD (i.e. CHD and/or stroke) events in patients in the individual and combined risk categories indicated in **Fig. 1** compared to those not in these areas. For example, patients in area (b + c) were compared to patients in other areas. Analysis was performed using either Japanese or Asian WC cut-off values. In general, especially in female patients, substantially greater risk assessment accuracy was achieved when using the Asian WC cut-off value than the Japanese valve, since a relatively large number of categories with significantly elevated hazard ratios were obtained when the Asian cut-off value was used. Moreover, hazard ratio values were generally higher when using the Asian WC cut-off value.

When the risk for patients included in an individual category (i.e., a b, c, d, e, f, or g) was calculated separately from risks for patients not included in that particular area, male patients with all three MetS components (i.e. area c) had a significantly increased risk, regardless of the WC threshold. Male patients in area f also had a significantly elevated risk, but only when the Asian WC cut-off value was applied; however, in female patients, none of the individual categories represented a significantly increased risk.

When risks in male patients included in combinations of two areas (i.e., (b + c), (c + d) or (c + f)) were assessed and compared with those not included in such combinations of those areas, only men in areas (c + d) and (c + f) had a significantly elevated hazard ratio.

Similarly, when men in areas (b + c + d), (b + c + f) or (c + d + f) were assessed against those in the complement set of each area, men in areas (b + c + f) and (c + d + f) had a significantly elevated risk. In female patients, a substantially different risk profile was obtained in combinations of two or three areas. For example, the hazard ratios for categories (b + c), (b + c + d) and (b + c + f) were significantly elevated to approximately twice that in those in the comple-

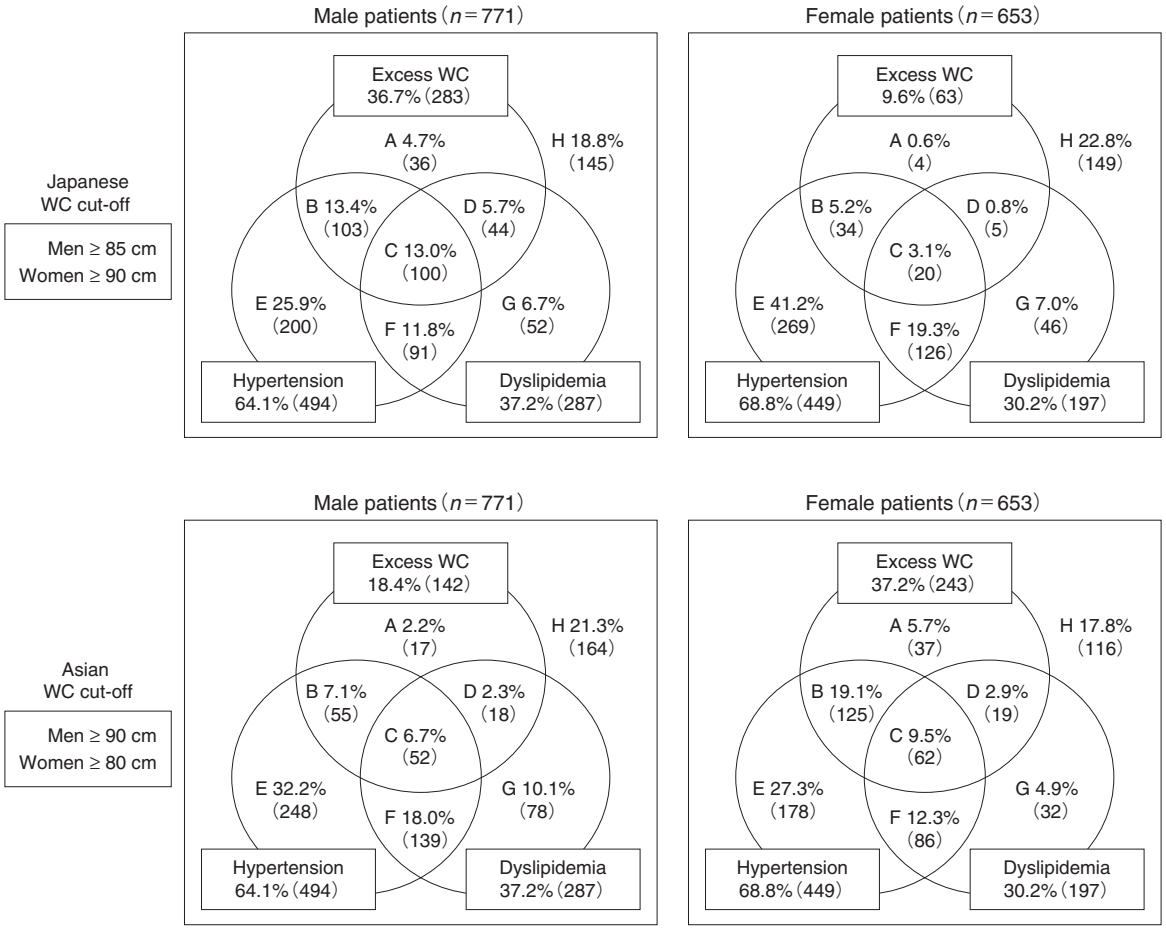

Fig. 1. Distribution of Japanese patients with type 2 diabetes categorized by baseline status of risk factor(s) (excess waist circumference (WC), hypertension and dyslipidemia).

ment set of each area. The current Japanese criteria of MetS[20] (corresponding to patients in area (b + c + d)) were predictive of CVD events only in female patients when the Asian WC cut-off value was applied.

When risks in patients included in a combination of four areas (b + c + d + f) were assessed, both male and female patients had significantly elevated hazard ratios when using the Asian cut-off value. The hazard ratio values were similar to those with combinations of two or three areas.

Discussion

The present analysis prospectively demonstrated in Japanese patients with type 2 diabetes that 1) at least two components of MetS in addition to hyperglycemia are required to have a significantly elevated CVD risk; 2) the combination of MetS components associated with a significantly elevated CVD risk is markedly different depending on gender and the WC cut-off value and 3) the combinations of MetS components with high hazard ratios for CVD did not completely agree with the current definitions of MetS. These findings imply that the current MetS criteria need to be modified when applied to patients with type 2 diabetes.

Although the clinical relevance in diagnosing MetS in diabetic subjects is still under debate[22], a simple assessment tool for cardiovascular risk in patients with diabetes but without an elevated LDL cholesterol level or who do not smoke is greatly needed in clinical settings, as demonstrated by the numerous recent studies that compared the hazard ratio for CVD between diabetic patients with and without MetS[1, 2, 4-13]; unfortunately, the results were inconsistent.

Some of these studies concluded that MetS diagnosed by the current definitions has a considerable role in the increased CVD risk in patients with type 2 diabetes[5, 6, 9, 12, 13], and that the impact of diabetes itself on CVD risk is relatively limited without coex-

Table 2. Hazard ratio of CVD events (CHD and/or stroke) in diabetic patients according to individual and combined risk categories indicated in Fig. 1 compared to those not in these categories

Threshold	Japanese cut-off value				Asian cut-off value			
	Men ≥85 cm		Women ≥90 cm		Men ≥90 cm		Women ≥80 cm	
Patient category	Hazard ratio (95% C.I.)	*p* value[§]	Hazard ratio (95% C.I.)	*p* value[§]	Hazard ratio (95% C.I.)	*p* value[§]	Hazard ratio (95% C.I.)	*p* value[§]
a	0.54 (0.13–2.21)	0.39	n/a[¶]		n/a[¶]		n/a[¶]	
b	0.68 (0.31–1.48)	0.33	2.27 (0.90–5.75)	0.08	0.94 (0.38–2.33)	0.89	1.71 (0.90–3.26)	0.10
c	2.05 (1.18–3.57)	0.01	n/a[¶]		2.25 (1.12–4.54)	0.02	1.91 (0.85–4.28)	0.12
d	1.39 (0.56–3.45)	0.48	n/a[¶]		1.33 (0.33–5.42)	0.69	1.88 (0.46–7.78)	0.38
e	0.80 (0.46–1.39)	0.43	0.74 (0.40–1.36)	0.34	0.69 (0.40–1.17)	0.17	0.54 (0.25–1.15)	0.11
f	1.64 (0.88–3.05)	0.12	1.90 (1.00–3.61)	0.05	1.73 (1.03–2.93)	0.04	1.11 (0.47–2.61)	0.82
g	0.61 (0.19–1.94)	0.40	1.65 (0.65–4.17)	0.29	0.85 (0.37–1.97)	0.71	1.27 (0.39–4.10)	0.69
b + c	1.34 (0.82–2.20)	0.24	1.33 (0.52–3.37)	0.55	1.57 (0.88–2.82)	0.13	2.06 (1.14–3.71)	0.02
c + d	1.97 (1.18–3.27)	0.01	–	0.99	2.06 (1.08–3.91)	0.03	1.98 (0.95–4.11)	0.07
c + f	2.12 (1.32–3.41)	0.00	1.53 (0.80–2.91)	0.20	2.12 (1.32–3.41)	0.00	1.53 (0.80–2.91)	0.20
b + c + d*	1.42 (0.88–2.28)	0.15	1.22 (0.48–3.09)	0.67	1.57 (0.90–2.73)	0.11	2.19 (1.22–3.93)	0.01
b + c + f	1.63 (1.03–2.58)	0.04	1.87 (1.03–3.40)	0.04	1.93 (1.22–3.07)	0.01	2.04 (1.13–3.68)	0.02
c + d + f	2.16 (1.36–3.43)	0.00	1.47 (0.77–2.79)	0.24	2.12 (1.33–3.39)	0.00	1.63 (0.88–3.04)	0.12
b + c + d + f	1.74 (1.01–2.77)	0.02	1.81 (1.00–3.29)	0.05	1.96 (1.23–3.11)	0.00	2.22 (1.21–4.05)	0.01

e.g., patients in area (b + c) were compared to patients in an area other than (b + c).
*corresponds to Japanese criteria of metabolic syndrome, [§]ANOVA, [¶]could not calculate because of no events

isting MetS or its components[23]. In contrast, in Finnish women[11] and Singaporean men[24], MetS diagnosed by existing criteria does not present a further risk of CVD in addition to that presented by type 2 diabetes per se. Likewise, combinations of any two MetS components were not significantly associated with higher mortality in Italian patients with type 2 diabetes[7, 25] and a single component of MetS was a more powerful predictor than the overall syndrome in Type 1 diabetic patients[26]. Similarly, a recent report of the United Kingdom Prospective Diabetes Study[4] also questioned the clinical value of diagnosing MetS for CVD risk stratification in patients newly diagnosed with type 2 diabetes.

These inconsistencies in previous prospective studies along with our current results suggest that the established definitions of MetS leave room for improvement when applied to diabetic patients. It also implies that specific combinations of MetS components that increase CVD risk in diabetic patients differ depending on the ethnic group; therefore, an ethnicity-specific definition of MetS might be necessary.

The current results also revealed gender differences in combinations of MetS components associated with higher CVD risks. In male patients, dyslipidemia had a relatively large prognostic value since area [c + (d and/or f)] indicated a significantly elevated risk for CVD events. On the other hand, in female patients, hypertension was important, which was similar to the result reported in Chinese patients with type 2 diabetes[10]. A large gender difference was also seen in other cohorts[11, 24, 27]. Most studies did not stratify results by gender in their analysis, which is considered to be a of the low prognostic power of the established definition of MetS; however, the gender difference became insignificant when area (b + c + d + f) in **Fig. 1** is considered.

The current results also indicated that the Asian WC cut-off value is more appropriate than the Japanese cut-off value, even for Japanese diabetic patients, for discriminating patients at high risk; however, WC per se was not indispensable for predicting CVD events in our patients despite the worldwide definition of IDF[21] as well as Japanese[20] definitions of MetS, as we reported previously[2]. The poor prognostic power of the IDF definition in diabetic subjects has also been reported for other ethnic groups, such as Hong Kong Chinese[5], Native Americans[6] and Italians[7]. Lack of a rationale for excess WC as a mandatory component of MetS was also shown in recent studies of non-diabetic subjects[14, 28].

Table 3 shows the suggested definitions of MetS for Japanese patients with type 2 diabetes based on our current and previous results. This criteria is similar

Table 3. Suggested definition of MetS for Japanese patients with type 2 diabetes for predicting future CVD events

Patients with two or more of the following
1) Excess WC: men ≥90 cm, women ≥80 cm
2) Hypertension: systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or use of an agent for this condition
3) Dyslipidemia: triglyceride ≥150 mg/dL and/or HDL-cholesterol <40 mg/dL or use of an agent for this condition

to that of the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI)[19] (revised version of NCEP-ATPⅢ) but differs in terms of dyslipidemia. that is, an elevated triglyceride level and decreased HDL cholesterol level were treated as individual components in the AHA/NHLBI definition. We previously determined that hazard ratios of hypertriglyceridemia alone and hypertriglyceridemia or low HDL cholesterol were almost identical, but the latter covers more patients. These two indices are known to be frequently correlated and so could have greater prognostic power when combined.

Monami and colleagues[8] suggested that a MetS diagnosis based only on the unweighted number of components present in each patient, without considering each specific combination, could be inadequate to predict the risk level because a different risk profile is determined by different combinations of metabolic alterations. Although our current results principally support their conclusion, we still consider that using area (b + c + d + f) in **Fig. 1** as a definition of MetS has merit in clinical settings because 1) the hazard ratios are similar (or even higher in female patients) to other significant combinations, 2) it can be used regardless of patient gender, 3) it covers more subjects than combinations of two or three areas among b, c, d and f, and 4) it is simple and easy to remember.

The current study has several strengths and limitations. The strengths include the nationwide multicentered setting and prospective design, which enabled us to assess the predictability of a CVD event. In addition, all institutes that participated are university or large general hospitals; therefore, the quality of risk evaluation and the accuracy of CVD diagnosis were excellent. A limitation is that the results may only be applicable to Japanese patients with type 2 diabetes. As described above, ethnicity can be considered an important factor for determining CVD risk in diabetic subjects as well as in the general population, so the clinical significance of MetS should be determined separately in each ethnic group. In addition, we do not have sufficient data on mortality, which needs to be determined in the future. We did not determine different cut-off values for blood pressure and serum lipids since their cut-off values have been well-established in many guidelines, unlike WC.

In conclusion, Japanese diabetic patients with two or more features of MetS with excess WC according to the Asian cut-off value (male ≥90 cm, female ≥80 cm), hypertension and dyslipidemia have a significantly elevated CVD event risk. Nevertheless, the rationale was weak for including WC as a mandatory component when evaluating CVD risk despite existing definitions of MetS. The definition of MetS should be modified to provide better prognostic value in clinical settings of diabetes management.

Appendix

The Japan Diabetes Complications Study (JDCS) Group:

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Acknowledgements

The Japan Diabetes Complications Study (JDCS) was financially supported by the Ministry of Health, Labor, and Welfare of Japan (H19-022). We gratefully acknowledge all of the patients, physicians and staff who took part in the JDCS.

References

1) Sone H, Mizuno S, Fujii H, Yoshimura Y, Yamasaki Y, Ishibashi S, Katayama S, Saito Y, Ito H, Ohashi Y, Akanuma Y, Yamada N: Japan Diabetes Complications Study: Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in asian diabetic patients? Analysis from the Japan Diabetes Complications Study. Diabetes Care, 2005; 28:1463-1471
2) Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito Y, Ohashi Y, Akanuma Y, Yamada N: The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions: additional analysis from the Japan Diabetes Complications Study. Diabetes Care, 2006; 29:145-147
3) Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito Y, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Comlications Study (JDCS) Group: The new worldwide definition of Metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitional analysis from the Japan Diabetes Complications Study. Diabetes Care, 2006; 29:145-147
4) Cull CA, Jensen CC, Retnakaran R, Holman RR: Impact of the metabolic syndrome on macrovascular and microvascular outcomes in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study 78. Circulation, 2007; 116:2119-2126
5) Tong PC, Kong AP, So WY, Yang X, Ho CS, Ma RC, Ozaki R, Chow CC, Lam CW, Chan JC, Cockram CS: The usefulness of the International Diabetes Federation and the National Cholesterol Education Program's Adult Treatment Panel Ⅲ definitions of the metabolic syndrome in predicting coronary heart disease in subjects with type 2 diabetes. Diabetes Care, 2007; 30:1206-1211
6) de Simone G, Devereux RB, Chinali M, Best LG, Lee ET, Galloway JM, Resnick HE: Prognostic impact of metabolic syndrome by different definitions in a population with high prevalence of obesity and diabetes: the Strong Heart Study. Diabetes Care, 2007; 30:1851-1856
7) Monami M, Marchionni N, Masotti G, Mannucci E: IDF and ATP-Ⅲ definitions of metabolic syndrome in the prediction of all-cause mortality in type 2 diabetic patients. Diabetes Obes Metab, 2007; 9:350-353
8) Monami M, Lambertucci L, Ungar A, Pieri M, Masotti G, Marchionni N, Mannucci E: Is the third component of metabolic syndrome really predictive of outcomes in type 2 diabetic patients? Diabetes Care, 2006; 29:2515-2517
9) Hillier TA, Rizzo JH, Pedula KL, Cauley JA, Schwartz AV, Ensrud KE, Browner WS: Increased mortality associ-

ated with the metabolic syndrome in older women with diabetes. Diabetes Care, 2005; 28:2258-2260
10) Ko GT, So WY, Chan NN, Chan WB, Tong PC, Li J, Yeung V, Chow CC, Ozaki R, Ma RC, Cockram CS, Chan JC: Prediction of cardiovascular and total mortality in Chinese type 2 diabetic patients by the WHO definition for the metabolic syndrome. Diabetes Obes Metab, 2006; 8:94-104
11) Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Proteinuria and metabolic syndrome as predictors of cardiovascular death in non-diabetic and type 2 diabetic men and women. Diabetologia, 2006; 49:56-65
12) Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA: Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med, 2006; 166:106-111
13) Guzder RN, Gatling W, Mullee MA, Byrne CD: Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes. Diabetologia, 2006; 49:49-55
14) Mancia G, Bombelli M, Corrao G, Facchetti R, Madotto F, Giannattasio C, Trevano FQ, Grassi G, Zanchetti A, Sega R: Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension, 2007; 49:40-47
15) Hanefeld M, Koehler C, Gallo S, Benke I, Ott P: Impact of the individual components of the metabolic syndrome and their different combinations on the prevalence of atherosclerotic vascular disease in type 2 diabetes: the Diabetes in Germany (DIG) study. Cardiovasc Diabetol, 2007; 26:6-13
16) Guize L, Thomas F, Pannier B, Bean K, Jego B, Benetos A: All-cause mortality associated with specific combinations of the metabolic syndrome according to recent definitions. Diabetes Care, 2007; 30:2381-2387
17) Sone H, Katagiri A, Ishibashi S, Abe R, Saito Y, Murase T, Yamashita H, Yajima Y, Ito H, Ohashi Y, Akanuma Y, Yamada N; JD Study Group: Effects of lifestyle modifications on patients with type 2 diabetes: the Japan Diabetes Complications Study (JDCS) study design, baseline analysis and three year-interim report. Horm Metab Res, 2002; 34:509-515
18) Organization WH: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Genova, Switzerland: Department of non-communicable Disease Surveillance; 1999,
19) Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation, 2005; 112:2735-2752
20) Definition and the diagnostic standard for metabolic syndrome--Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Nippon Naika Gakkai Zasshi, 2005; 94:794-809
21) Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group: The metabolic syndrome--a new worldwide definition. Lancet, 2005; 366:1059-1062
22) Fujita T: The metabolic syndrome in Japan. Nature Clinical Practice, 2008; 5 Suppl 1:S15-18
23) Liu J, Grundy SM, Wang W, Smith SC Jr, Vega GL, Wu Z, Zeng Z, Wang W, Zhao D: Ten-year risk of cardiovascular incidence related to diabetes, prediabetes, and the metabolic syndrome. Am Heart J, 2007; 153:552-558
24) Mak KH, Ma S, Heng D, Tan CE, Tai ES, Topol EJ, Chew SK: Impact of sex, metabolic syndrome, and diabetes mellitus on cardiovascular events. Am J Cardiol, 2007; 100:227-233
25) Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P; Casale Monferrato Study: Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. Diabetes Care, 2004; 27:2689-2694
26) Pambianco G, Costacou T, Orchard TJ: The prediction of major outcomes of type 1 diabetes: a 12-year prospective evaluation of three separate definitions of the metabolic syndrome and their components and estimated glucose disposal rate: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes Care, 2007; 30:1248-1254
27) Hunt KJ, Williams K, Hazuda HP, Stern MP, Haffner SM: The metabolic syndrome and the impact of diabetes on coronary heart disease mortality in women and men: the San Antonio Heart Study. Annals of Epidemiology, 2007; 17:870-877
28) Lee J, Ma S, Heng D, Tan CE, Chew SK, Hughes K, Tai ES: Should central obesity be an optional or essential component of the metabolic syndrome? Ischemic heart disease risk in the Singapore Cardiovascular Cohort Study. Diabetes Care, 2007; 30:343-347