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

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We previously reported (1) the limited clinical significance for Japanese diabetic patients of the widely used World Health Organization (WHO) (2) and National Cholesterol Education Program (NCEP) (3) definitions of metabolic syndrome and suggested that an international definition of metabolic syndrome that was applicable regardless of ethnicity was necessary (1).

Recently, the International Diabetes Federation published a long-awaited new worldwide definition of metabolic syndrome (4) that is intended to be applicable to various ethnic groups. The new definition is similar to the NCEP definition (3) but has several important differences. Notably, most components of the new definition now include subjects who are receiving specific treatments for the abnormalities that comprise metabolic syndrome. Also, central obesity (defined by waist circumference with ethnic modification in its thresholds) has become a mandatory component in the new definition. In this report, we evaluated the predictive power of the new international definition for cardiovascular disease (CVD), as compared with that of previous definitions, in Japanese diabetic patients.

RESEARCH DESIGN AND METHODS — The Japan Diabetes Complications Study (JDCS) has been described in detail elsewhere (1,5). The same dataset was used for evaluation so that the new definition of metabolic syndrome could be directly compared with the WHO and NCEP definitions (1–4). A total of 1,424 Japanese patients (771 men and 653 women, age 58.4 ± 7.4 years [means ± SD]) with previously diagnosed type 2 diabetes but without known CVD were followed for 8 years for coronary heart disease (CHD) and stroke events. Fatal and nonfatal CHD and stroke were defined as previously reported (1). The new International Diabetes Federation definition (4) was used with a recommended ethnic modification for Japanese subjects in relation to waist circumference (men ≥85 cm, women ≥90 cm). Since all of the subjects had diabetes, metabolic syndrome diagnosis was made in patients who met criteria for central obesity plus one or more of the following: increased triglycerides, increased blood pressure, or reduced HDL cholesterol (see Table 1 for detailed thresholds). Incidence rates in the two groups (with and without metabolic syndrome) were estimated under the Poisson assumption using person-year methods. Cox regression analysis was used to calculate the age-adjusted hazard ratio (HR) and 95% CI of metabolic syndrome risk factors with CHD, stroke, or both. The SAS software package (version 8.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered statistically significant.

RESULTS — At baseline, the prevalence of metabolic syndrome, using the new definition (Table 1), was notably lower, especially in female patients, than the prevalence under the WHO (2) and NCEP (3) definitions, which was ~50% on average (1). Diabetes duration in patients with (9.9 ± 6.9 years) or without (10.7 ± 7.3 years) metabolic syndrome did not differ significantly ($P = 0.07$). The proportion of patients that met the central obesity criterion (an essential component of the new definition) was 36.7% for men and 9.7% for women, such that 87% of men and 95% of women with central obesity had metabolic syndrome.

The incidence (per 1,000 patient-years) of CHD (13.5 [with metabolic syn-

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JDCS, Japan Diabetes Complications Study; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

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

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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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: Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in Asian diabetic patients? Analysis from the Japan Diabetes Complications Study. *Diabetes Care* 28:1463–1471, 2005
2. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus.* Geneva, World Health Org., 1999
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

(Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
4. The International Diabetes Federation: The IDF consensus worldwide definition of metabolic syndrome [article online], 2005. Available from http://www.idf.org/webdata/docs/IDF_metasyndrome_definition.pdf. Accessed 10 July 2005
5. Sone H, Katagiri A, Ishibashi S, Abe R, Saito Y, Murase T, Yamashita H, Yajima Y, Ito H, Ohashi Y, Akanuma Y, Yamada N, the 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* 34:509–515, 2002
6. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
7. Gimeno Orna JA, Lou Arnal LM, Molinero Herguedas E, Boned Julian B, Portilla Cordoba DP: Metabolic syndrome as a cardiovascular risk factor in patients with type 2 diabetes. *Rev Esp Cardiol* 57:507–513, 2004 [article in Spanish]
8. Bonora E, Targher G, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Gemma L, Santi L, Bonadonna RC, Muggeo M: Metabolic syndrome is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabet Med* 21:52–58, 2004
9. Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P: Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes: the Casale Monferrato Study. *Diabetes Care* 27:2689–2694, 2004
10. Ford ES: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 28:1769–1778, 2005
11. Reynolds K, Muntner P, Fonseca V: Metabolic syndrome: underrated or underdiagnosed? *Diabetes Care* 28:1831–1832, 2005
12. Jorgensen ME, Borch-Johnsen K: The metabolic syndrome: is one global definition possible? *Diabet Med* 21:1064–1065, 2004
13. Tan CE, Ma S, Wai D, Chew SK, Tai ES: Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 27:1182–1186, 2004
14. Mandavilli A, Cyranoski D: Asia's big problem. *Nat Med* 10:325–327, 2004
15. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D: Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA* 291:2591–2599, 2004
16. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N, the Japan Diabetes Complication Study Group: Obesity and type 2 diabetes in Japanese patients (Letter). *Lancet* 361:85, 2003
17. Sone H, Yamada N, Mizuno S, Aida R, Ohashi Y: Alcohol use and diabetes mellitus (Letter). *Ann Intern Med* 141:408–409, 2004
18. Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N, the Japan Diabetes Complications Study Group: Energy intake and obesity in Japanese patients with type 2 diabetes (Letter). *Lancet* 363:248–249, 2004
19. Sone H, Mizuno S, Yamada N: Vascular risk factors and diabetic neuropathy (Letter). *N Engl J Med* 352:1925–1927, 2005