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

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OBJECTIVE — The purpose of this study was to compare the predictive value for coronary heart disease (CHD) of the International Diabetes Federation (IDF) definition (with Asian criteria for central obesity) of the metabolic syndrome with existing criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in Chinese subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Subjects with type 2 diabetes and without macrovascular diseases or end-stage renal disease were categorized by the criteria of the IDF and the NCEP ATP III. CHD was defined as myocardial infarction, ischemic heart disease, coronary revascularization, heart failure, and death related to CHD.

RESULTS — Of 4,350 patients (aged 54.4 ± 13.4 years; median follow-up period 7.1 [interquartile range 5.2–8.5] years), 65.9% had metabolic syndrome according to either IDF or NCEP ATP III criteria. The NCEP ATP III definition identified metabolic syndrome in 786 subjects (18.1%) who did not fulfill the criteria of the IDF. HDL cholesterol and systolic blood pressure were predictors of CHD after adjustment for other confounding factors. Compared with subjects without metabolic syndrome, the IDF criteria failed to predict CHD (hazard ratio 1.13 [95% CI 0.86–1.48], $P = 0.374$). In contrast, the NCEP ATP III definition (2.51 [1.80–3.50], $P < 0.001$) predicted an increased risk of CHD with the NCEP-only group having the highest risk (2.49 [1.66–3.73], $P < 0.001$).

CONCLUSIONS — With established type 2 diabetes, the IDF definition of the metabolic syndrome failed to identify a subgroup of patients who had the highest risk for CHD. Practitioners must recognize the appropriate setting for its application.

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Coexistence of glucose intolerance, central obesity, insulin resistance, hypertension, dyslipidemia, proinflammatory state, gout, and albuminuria is associated with premature atherosclerosis and coronary heart disease (CHD) (1–3) as well as type 2 diabetes (4,5). The constellation of these conditions is known as the metabolic syndrome. Various criteria have been proposed by the World Health Organization (WHO) (6), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (7), and the European Group for the Study of Insulin Resistance (8) to define the clustering of such risk factors in individuals. There are essential components that are common to all definitions, such as glucose intolerance, obesity, hypertension, and dyslipidemia, although the exact criteria differ among definitions. For subjects without diabetes, the need for assessment of insulin resistance by either an oral glucose tolerance test or the hyperinsulinemic-euglycemic clamp implies that the WHO definition is more appropriate for clinical research purposes. In contrast, the NCEP ATP III definition is better suited for clinical practice because it only requires measurement of fasting blood glucose (9). Furthermore, given the difference in adiposity among different populations, the cutoff points for obesity in the WHO and NCEP ATP III definitions have been questioned (10,11). To provide a more clinician-friendly definition for the metabolic syndrome than the original

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Abbreviations: ACR, albumin-to-creatinine ratio; ATP III, Adult Treatment Panel III; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IDF, International Diabetes Federation; 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.

WHO criteria, the International Diabetes Federation (IDF) has proposed a new definition (12). The cutoff values for blood pressure, HDL cholesterol, and triglycerides have been revised to ensure consistency with the NCEP ATP III criteria. Central obesity was accepted as a prerequisite risk factor for the diagnosis of the syndrome. Specific values for waist circumference are recommended to acknowledge the difference in adiposity among different ethnic groups. Similar to the NCEP ATP III definition, the IDF definition does not include insulin resistance in the criteria.

Controversies continue as to whether the metabolic syndrome is really a discrete syndrome adding predictive value over and above the sum of its components (13,14). It may be that the different criteria and definitions do offer such additional value but not in all settings or even in the same settings for each criterion. In particular, the usefulness of applying the definition of metabolic syndrome among subjects with known diabetes in predicting adverse cardiovascular events has not been fully elucidated. Therefore, the predictability of the IDF and NCEP ATP III criteria for metabolic syndrome on the development of CHD in a cohort of Chinese subjects who have already developed type 2 diabetes was examined.

RESEARCH DESIGN AND METHODS

— Patients with diabetes were referred from general practitioners, general medical clinics, and other specialist clinics of the hospital to the Prince of Wales Hospital Diabetes Centre and underwent comprehensive assessment of complications and risk factors on the basis of the European DIABCARE protocol (15). Between 1995 and 2000, 5,190 patients were assessed. Patients with type 1 diabetes ($n = 324$), defined as acute presentation with diabetic ketoacidosis, heavy ketonuria (>3+), or continuous requirement of insulin within 1 year of diagnosis, were excluded from this analysis. Patients with macrovascular complications and estimated glomerular filtration rate (eGFR) <15 ml/min per 1.73 m^2 were not included ($n = 412$). The presence or absence of metabolic syndrome could not be established in 104 patients because of incomplete data collection. Hence, 4,350 patients were included in the final analysis. Informed consent was obtained from all patients at the time of assessment to allow use of data for research purposes. The study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

Details of the assessment and laboratory measurement of metabolic parameters were described previously (16). All patients had at least two urinary collections: a sterile, random spot urine sample was used to measure albumin-to-creatinine ratio (ACR) followed by a timed collection (4 or 24 h) for measurement of ACR. The definition of albuminuria was based on the mean value of ACR from both the timed and spot urinary samples. Normoalbuminuria was defined as a mean ACR ≤3.5 mg/mmol, microalbuminuria was defined as ACR between 3.5 and 25 mg/mmol, and macroalbuminuria was defined as ACR ≥25 mg/mmol (17). eGFR (expressed in milliliters per minute per 1.73 meters squared) was calculated using the abbreviated modification of diet in renal disease formula further adjusted for the Chinese ethnicity (18):

$$\text{eGFR} = 186 \times [S_{Cr} \times 0.011]^{-1.154} \times [\text{age}]^{-0.203} \times 0.742 \text{ [if female] or} \times 1.233 \text{ [if Chinese]}$$

where S_{Cr} is serum creatinine expressed in micromoles per liter. Chronic kidney disease was defined by eGFR <60 ml/min per 1.73 m^2.

Diagnostic criteria of metabolic syndrome

Metabolic syndrome was diagnosed according to the NCEP ATP III and IDF criteria. For this cohort, all subjects fulfilled one criterion of the metabolic syndrome, namely previously diagnosed as having type 2 diabetes. The definitions for metabolic syndrome are listed as follows:

1) NCEP ATP III criteria: three or more of the following conditions:
   a) Central obesity: waist circumference >102 cm (male) or >88 cm (female)
   b) Raised triglyceride level: ≥1.7 mmol/l or specific treatment for this lipid abnormality
   c) Reduced HDL cholesterol: <1.03 mmol/l (male) or 1.29 mmol/l (female)
   d) Raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension
   e) Previously diagnosed type 2 diabetes

2) IDF criteria: for a individual to be classified as having the metabolic syndrome, he or she must have central obesity, defined by the Chinese specific waist circumference cutoffs (male ≥90 cm or female ≥80 cm) plus any two of the following four factors:
   a) Raised triglyceride level: ≥1.7 mmol/l or specific treatment for this lipid abnormality
   b) Reduced HDL cholesterol: <1.03 mmol/l (male) or 1.29 mmol/l (female)
   c) Raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension
   d) Previously diagnosed type 2 diabetes

Clinical outcomes

Hong Kong has a heavily subsidized health care system, and 95% of inpatient and chronic care is provided by the Hospital Authority hospitals. All end points including hospital admissions and mortality were censored on 30 July 2005 using databases from the Hospital Authority Central Computer System, which records admissions to all public hospitals. These databases, including the Hong Kong Death Registry, were matched by a unique identification number, the Hong Kong Identity Card number, which is compulsory for all residents in Hong Kong. With use of the ICD-9 code, CHD was defined as *1*) acute myocardial infarction (code 410) or death due to a coronary cause (codes 410, 411–414, and 428) and *2*) other nonfatal CHD (codes 411–414 and procedure codes 36 and 00.66).

Statistical analysis

The analysis was performed using the SPSS (version 11.5). Triglyceride levels and ACR were logarithmically transformed because of skewed distributions. All data are expressed as means ± SD or median [interquartile range], as appropriate. The Student's t test or ANOVA was used for between-group comparisons for continuous variables, and the χ^2 test was used for categorical variables. Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) with 95% CI for clinical end points. A forward stepwise algorithm ($P < 0.10$ for entry and $P < 0.05$ for stay) was used.

Table 1—*Clinical and metabolic characteristics of 4,350 Chinese patients with type 2 diabetes divided according to different definitions of the metabolic syndrome*

	Metabolic syndrome			
	NCEP-only	IDF/NCEP	IDF-only	No
n (%)	786 (18.1)	1,628 (37.4)	454 (10.4)	1,482 (34.1)
Male sex (%)	52.5	30.0*	44.3†	51.9
Smoking status (%)				
Never	69.4	77.3	75.1	70.8
Ex-smoker	15.2	12.3	14.3	15.4
Current smoker	15.4	10.4	10.6	13.8
Age (years)	55.9 ± 12.4	56.3 ± 13.4	54.9 ± 13.7	51.3 ± 13.3†
Duration of diabetes (years)	7.1 ± 6.6	7.2 ± 6.5	6.6 ± 6.1	6.5 ± 6.0
Waist (cm)				
Men	83.8 ± 4.5	98.5 ± 8.0†	94.7 ± 3.4†	82.1 ± 7.5†
Women	74.6 ± 3.6	90.4 ± 7.3†	83.7 ± 2.5†	75.7 ± 8.2‡
BMI (kg/m^2)	22.9 ± 2.3	27.8 ± 3.8†	26.1 ± 2.6†	22.9 ± 3.2
Systolic blood pressure (mmHg)	138 ± 20	142 ± 19†	135 ± 11	124 ± 18†
Diastolic blood pressure (mmHg)	79 ± 11	80 ± 11*	78 ± 11	73 ± 10†
A1C (%)	7.95 ± 1.94	7.88 ± 1.67	7.49 ± 1.67†	7.58 ± 2.01†
FPG (mmol/l)	9.2 ± 3.6	9.0 ± 3.2	8.5 ± 2.8‡	8.4 ± 2.8†
Total cholesterol (mmol/l)	5.66 ± 1.40	5.58 ± 1.18	5.11 ± 0.93†	5.06 ± 0.96†
HDL cholesterol (mmol/l)				
Men	1.03 ± 0.27	1.02 ± 0.27	1.22 ± 0.28†	1.34 ± 0.33†
Women	1.24 ± 0.36	1.19 ± 0.28	1.45 ± 0.35†	1.57 ± 0.38†
LDL cholesterol (mmol/l)	3.57 ± 1.09	3.47 ± 0.99	3.20 ± 0.80†	3.15 ± 0.84†
Triglycerides (mmol/l)	1.76 (1.19–2.44)	1.89 (1.32–2.64)†	1.13 (0.87–1.43)†	0.94 (0.71–1.20)†
Serum creatinine (μmol/l)				
Men	85 (76–100)	89 (77–109)	84 (74–94)*	83 (73–93)†
Women	65 (56–79)	67 (58–80)	62 (55–71)†	59 (53–68)†
eGFR (ml/min per 1.73 m^2)	108 ± 34	106.0 ± 35.0	115 ± 30†	121 ± 32†
Spot ACR (mg/mmol)	1.9 (0.8–10.0)	3.2 (1.0–17.0)†	1.6 (0.7–5.5)†	1.1 (0.6–3.0)†
Complications at baseline				
Microalbuminuria (%)	26.5	33.0†	25.2	19.3†
Macroalbuminuria (%)§	21.8	19.4†	7.9†	5.3†
Retinopathy (%)§	26.2	25.5	20.5‡	17.7†
Neuropathy (%)	25.2	27.9	26.5	22.4
Chronic kidney disease (%)§	9.0	9.0	3.0†	3.7†

Data are mean ± SD or median (interquartile range). Chronic kidney disease was defined as eGFR <60 ml/min per 1.73m^2. *$P < 0.01$ vs. subjects with metabolic syndrome (NCEP-only). †$P < 0.001$ vs. subjects with metabolic syndrome (NCEP-only). ‡$P < 0.05$ vs. subjects with metabolic syndrome (NCEP-only). §$P < 0.001$ for differences among groups, Pearson χ^2 test.

Variables included age, male sex, duration of diabetes, smoking history, A1C, fasting plasma glucose (FPG), albuminuria status, waist circumference, systolic and diastolic blood pressure, HDL cholesterol, and triglycerides. $P < 0.05$ (two-tailed) was considered to be significant.

RESULTS — In this cohort of 4,350 subjects (age [mean ± SD] 54.4 ± 13.4 years; median follow-up period 7.1 [interquartile range 5.2–8.5] years), 2,868 (65.9%) had metabolic syndrome defined by either IDF or NCEP ATP III criteria. Among those with metabolic syndrome, 1,628 (37.4%) fulfilled the criteria of both the IDF and NCEP ATP III (IDF/NCEP). For the remaining patients with metabolic syndrome, 454 (10.4%) and 786 (18.1%) met only the criteria of the IDF (IDF-only) or the NCEP ATP III (NCEP-only), respectively.

Table 1 lists the clinical and metabolic parameters according to categories of metabolic syndrome. Patients fulfilling NCEP-only were older and had longer known duration of diabetes and higher levels of A1C, FPG, total cholesterol, LDL cholesterol, serum creatinine, and ACR but lower eGFR compared with patients without metabolic syndrome. These subjects also had lower BMI; higher A1C, FPG, total cholesterol, LDL cholesterol, triglycerides, and ACR; and lower HDL cholesterol and eGFR compared with those fulfilling IDF-only. Furthermore, subjects fulfilling NCEP-only had higher rates of microvascular complications and chronic kidney disease at baseline.

The incidence of CHD for the entire cohort was 8.1 per 1,000 person-years [95% CI 7.0–9.1]. The rates for subjects with no metabolic syndrome, IDF-only, IDF/NCEP, and NCEP-only were 4.1 [2.8–5.3], 3.3 [1.2–5.3], 10.9 [9.0–12.9], and 12.2 [9.2–15.1] per 1,000 person-years, respectively ($P < 0.001$). To determine predictors of CHD, individual cardiovascular risk factors were entered in a forward stepwise Cox proportional hazard analysis model. Systolic blood pressure and HDL cholesterol were identified as independent predictors of CHD in addition to age, known duration of diabetes, smoking status, and albuminuria

Table 2—*Predictors of CHD in 4,350 Chinese patients with type 2 diabetes*

	HR	95% CI	*P*
Age (per year)	1.02	1.01–1.03	0.002
Known duration of diabetes (per year)	1.04	1.02–1.06	<0.001
Smoking status			
Never	1.00		
Ex-smoker	1.50	1.07–2.11	0.019
Current smoker	1.91	1.34–2.71	<0.001
Albuminuric status			
Normoalbuminuria	1.00		
Microalbuminuria	1.74	1.25–2.34	<0.001
Macroalbuminuria	2.24	1.55–3.23	<0.001
Systolic blood pressure (per 10 mmHg)	1.10	1.03–1.18	0.004
HDL cholesterol (per mmol/l)	0.52	0.35–0.79	0.002

Other covariates not selected in the final model included male sex, FPG, A1C, diastolic blood pressure, waist circumference, and triglyerides.

status. Neither triglyceride level nor waist circumference was selected by the model (Table 2).

The discriminative power of different definitions of metabolic syndrome was examined by substituting waist circumference, systolic and diastolic blood pressure, HDL cholesterol, and triglycerides with metabolic syndrome as defined by the IDF or NCEP ATP III criteria. After adjustment for other confounding factors, the IDF definition of metabolic syndrome failed to predict CHD (HR 1.13 [95% CI 0.86–1.48], $P = 0.374$). In contrast, subjects with metabolic syndrome as defined by the NCEP ATP III definition had an increased risk (2.51 [1.80–3.50], $P < 0.001$) of developing adverse cardiovascular outcomes.

The predictive value among different definitions of metabolic syndrome of CHD was further delineated by categorizing the cohort of subject according to the IDF or NCEP ATP III criteria for metabolic syndrome. Patients fulfilling NCEP-only (HR 2.49 [1.66–3.73], $P < 0.001$) and IDF/NCEP (2.25 [1.54–3.30], $P < 0.001$) had increased risk of developing CHD compared with those without metabolic syndrome. Patients fulfilling IDF-only had a risk (0.78 [0.39–1.56], $P = 0.482$) of CHD similar to that of those without metabolic syndrome. The cumulative HR of CHD according to different definitions of metabolic syndrome is depicted in Fig. 1. The curves separated soon after the commencement of the follow-up period and continued to diverge with time ($P < 0.001$ for differences among groups).

CONCLUSIONS — In this cohort of subjects in whom type 2 diabetes already existed but who did not have macrovascular complications and end-stage renal disease at baseline, 65.9% had metabolic syndrome according to either NCEP ATP III or IDF criteria. The NCEP ATP III definition identified 18.1% of subjects with metabolic syndrome that was not identified by the IDF criteria. In contrast, 10.4% of subjects fulfilled the IDF definition only. Application of the IDF criteria for the metabolic syndrome failed to predict the development of CHD, whereas the NCEP ATP III definition of metabolic syndrome was an independent predictor of such events. Patients who were identified only by the NCEP ATP III definition had the highest risk of having CHD.

By using individual cardiovascular risk factors in the regression analysis, blood pressure and HDL cholesterol were identified as predictors of CHD. The finding of hypertension and dyslipidemia in predicting future CHD is in agreement with a study of Japanese patients with type 2 diabetes (14). Intriguingly, both waist circumference and triglyceride level were not selected in the final model. These findings may explain the better predictive role of the metabolic syndrome as defined by the NCEP ATP III criteria. It is noteworthy that the NCEP ATP III definition does not require the presence of central obesity as a prerequisite for diagnosis of metabolic syndrome. A diagnosis of diabetes implies that a patient requires the presence of two of five additional factors to fulfill the requirements of the NCEP ATP III definition. Therefore, the NCEP ATP III classification includes patients who do not have central obesity and yet have other components of the metabolic syndrome. It encompasses more diabetic patients with dyslipidemia (raised triglycerides and/or reduced HDL cholesterol) and hypertension, which are known risk factors for the development of CHD (19,20).

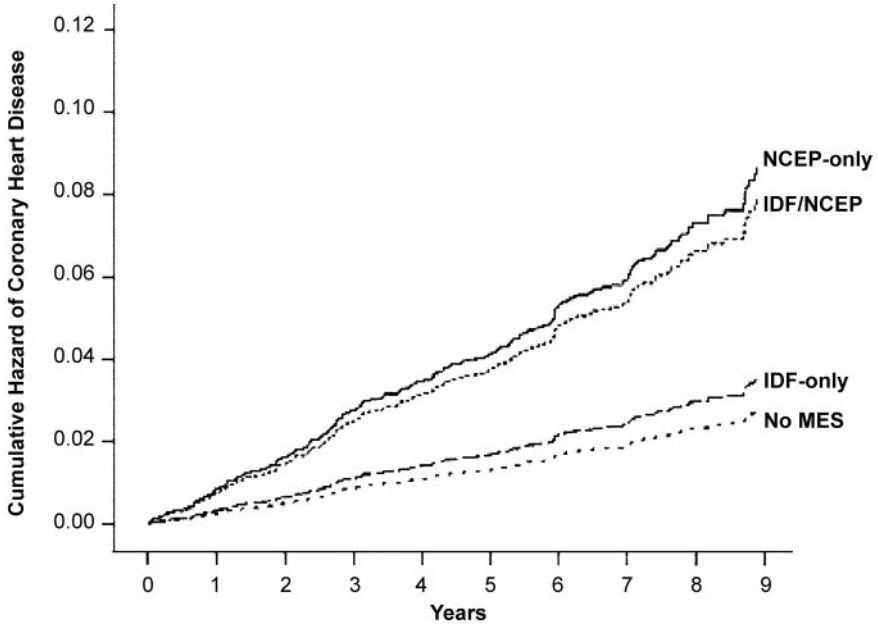

Figure 1—*Cumulative hazard of CHD according to different categories of the metabolic syndrome in 4,350 Chinese patients with type 2 diabetes using Cox regression analysis. Subjects were divided into those without metabolic syndrome (No MES), those fulfilling IDF criteria only (IDF-only), those fulfilling IDF and NCEP ATP III criteria (IDF/NCEP), and those fulfilling NCEP ATP III criteria only (NCEP-only). Other covariates included age, male sex, known duration of known diabetes, smoking, A1C, FPG, and albuminuric status at baseline.*

The IDF definition is more restrictive, requiring the presence of central obesity. Consequently, despite having hypertension and dyslipidemia, patients without central obesity will not be categorized as having the metabolic syndrome using the IDF criteria. For those individuals who did not have central obesity, the application of the NCEP ATP III criteria identified a subgroup (NCEP-only) at even higher risk of CHD. Individuals in the NCEP-only group were thinner and had worse glycemic control, lipid profiles, renal function, and albuminuria compared with individuals who only fulfilled the IDF criteria (IDF-only). Despite similar age and duration of known diabetes, subjects fulfilling NCEP-only had more diabetes complications at baseline and developed more adverse clinical events compared with those fulfilling IDF-only.

The difference in metabolic profiles suggests different prevailing factors in subjects fulfilling IDF-only or NCEP-only. Insulin resistance and visceral obesity are most likely to be present in patients with IDF-only. Despite having less central obesity, subjects fulfilling NCEP-only had poor glycemic control and a more adverse lipid profiles compared with those of the IDF-only or IDF/NCEP groups. Although this phenomenon may represent a form of "reverse epidemiology " with low BMI being associated with more comorbidities, low BMI and waist circumference had also been reported in insulin-deficient Chinese subjects with type 2 diabetes and correlated well with fasting C-peptide levels (21). Thus, the NCEP-only group may include patients with reduced pancreatic β-cell function, which is more common in the setting of low BMI and waist circumference. In this respect, insulin deficiency, poor glycemic control, and renal dysfunction are all known to promote catabolism of fat and muscle, resulting in a reduction in muscle mass and weight loss. Together with results from the Japanese Diabetes Complication Study (22), these findings support the notion that Asian patients with type 2 diabetes have a high risk of future cardiovascular events, irrespective of their central obesity.

Asian patients with type 2 diabetes have a very high prevalence of albuminuria of 60% (23). Albuminuria, a marker for both vascular and renal disease, is now recognized as a predictor for atherosclerosis and cardiovascular events (24–26). Results from the present study confirm that both micro- and macroalbuminuria were independent predictors, even in the presence of metabolic syndrome. Mechanisms underlying the association between albuminuria and cardiovascular disease include elevated levels of von Willebrand factor and other markers of endothelial dysfunction and increased transcapillary albumin leakage and platelet aggregability (27–29). Results from the present study also argue for the inclusion of albuminuria as a criterion of the metabolic syndrome as originally proposed by the WHO.

There are limitations to an observational study. First, there may be selection bias in recruiting patients. The Prince of Wales Hospital is a regional hospital serving a population of about 1.2 million. Most patients with chronic diseases including diabetes are managed at public hospitals in Hong Kong. Patients were referred from primary care physicians, general medical clinics, and the diabetes clinic of the Prince of Wales Hospital. The Diabetes Centre is the one place in the region where comprehensive complication screening is carried out. There were no specific referral criteria for this service apart from encouraging all patients to undergo comprehensive assessment at referral and periodically thereafter. Hence, this cohort is a true representation of patients with diabetes in the region. Second, the true incidence of CHD based on hospitalization records might have been underestimated because comprehensive cardiac assessments were not routinely performed in asymptomatic patients. Nevertheless, such underestimation of events would tend to attenuate rather than strengthen the observed associations. Furthermore, comprehensive cardiac assessments were not routinely performed in asymptomatic patients. The cardiovascular status at baseline was based only on medical record or typical symptoms in the presence of abnormal electrocardiograms or stress tests; we might have included patients with silent cardiovascular diseases. Furthermore, the effects of antidiabetes treatment and concomitant medications such as statins or renin-angiotensin system inhibitors were not included in the analysis. Lastly, all covariates were measured once at baseline. The variability of measurements may lead to underestimation of the confounding effect of covariates on outcomes.

The newly proposed IDF definition is a useful tool to identify subjects with a high risk for development of diabetes or cardiovascular disease and is supported by a large body of epidemiological data showing the importance of central obesity and associated insulin resistance in the general population. However, it remains to be proven whether these criteria have either predictive value for cardiovascular risk equivalent or superior to that of other definitions in different ethnic groups. Thus, results from our study suggest that the IDF definition of metabolic syndrome does not give additional prognostic value in the context of known and established type 2 diabetes. With the onset of diabetes and other complications, central obesity may become a less prominent feature and other risk factors, notably, albuminuria, may take on a more significant role. Thus, by inclusion of central obesity as a prerequisite in the IDF definition, the importance of other risk factors may not be acknowledged, as indicated by the better prognostic value of the NCEP ATP III than the IDF definition in our cohort. The less restrictive definition of the NCEP ATP III does, however, encompass these high-risk subjects with dyslipidemia and hypertension but not central obesity who, in fact, had the highest risk of CHD. The limitations of the IDF criteria for metabolic syndrome in predicting CHD have also been reported in general populations of white non-Hispanic men and Korean and European men and women (30–32). The present study further demonstrates the failure of the IDF criteria to identify metabolic syndrome in a subgroup of individuals who have a particularly high risk of development of CHD when diabetes is already present. Perhaps more attention should be paid to individual components of risk in patients with established type 2 diabetes, particularly those with albuminuria, hypertension, and low levels of HDL cholesterol.

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