

Metabolic Syndrome and Development of Diabetes Mellitus: Application and Validation of Recently Suggested Definitions of the Metabolic Syndrome in a Prospective Cohort Study

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Received for publication January 23, 2002; accepted for publication June 18, 2002.

The World Health Organization (WHO) and the National Cholesterol Education Program (NCEP) recently proposed definitions for the metabolic syndrome. Little is known of their validity, however. The authors assessed the sensitivity and specificity of the definitions of the metabolic syndrome for prevalent and incident diabetes mellitus in a Finnish population-based cohort of middle-aged men ($n = 1,005$) followed for 4 years since the late 1980s. Four definitions based on the WHO and NCEP recommendations were compared. All definitions identified persons at high risk for developing diabetes during the 4-year follow-up (odds ratios = 5.0–8.8). The WHO definition including waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m² was the most sensitive (0.83 and 0.67) and least specific (0.78 and 0.80) in detecting the 47 prevalent and 51 incident cases of diabetes. The NCEP definition in which adiposity was defined as waist girth > 102 cm detected only 61% of prevalent and 41% of incident diabetes, although it was the most specific (0.89 and 0.90). The WHO definition seems valid as judged by its relatively high sensitivity and specificity in predicting diabetes. The NCEP definition including waist > 102 cm also identifies persons at high risk for diabetes, but it is relatively insensitive in predicting diabetes.

diabetes mellitus; hyperinsulinism; hyperlipidemia; hypertension; insulin resistance; obesity

Abbreviations: EGIR, European Group for the Study of Insulin Resistance; HDL, high density lipoprotein; NCEP, National Cholesterol Education Program; QUICKI, quantitative insulin sensitivity check index; WHO, World Health Organization.

The concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia, and hypertension and its association with subsequent development of type 2 diabetes mellitus and cardiovascular disease has given rise to the concept of the metabolic syndrome, also known as the insulin resistance syndrome (1, 2). Insulin resistance is considered the underlying abnormality in this syndrome. The pathogenesis of this syndrome is still unclear, although environmental factors such as diet and physical activity, coupled with still largely unknown

genetic factors, clearly interact to produce the syndrome (1–3).

Despite abundant epidemiologic and experimental research that has been published on the metabolic syndrome, definitions of this syndrome and the various cutoffs for its components have varied widely (2). The World Health Organization (WHO) consultation for the classification of diabetes and its complications (4) and the National Cholesterol Education Program (NCEP) Expert Panel (5) recently published definitions of the metabolic syndrome.

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The WHO published a working definition meant to facilitate research on the metabolic syndrome and aid comparability between studies rather than serve as a strict definition (4). For men, the metabolic syndrome was defined (without assumptions of causality) as insulin resistance in the top 25 percent of the population as measured by the euglycemic hyperinsulinemic clamp or the presence of impaired glucose tolerance or type 2 diabetes and the presence of at least two of the following: abdominal obesity (waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m²), dyslipidemia (serum triglycerides ≥ 1.70 mmol/liter or high density lipoprotein (HDL) cholesterol < 0.9 mmol/liter), hypertension ($\geq 160/90$ mmHg), or microalbuminuria. These core components were considered most suitable for a general definition, although many other disturbances—for example, disorders of coagulation and endothelial function, hyperuricemia, and elevated leptin levels—have been associated with the metabolic syndrome (2).

This working definition has not been without criticism. Inclusion of microalbuminuria as a core component is controversial, and microalbuminuria in nondiabetic persons is uncommon (6–9). The most appropriate measure of abdominal obesity is also in dispute. Although the waist-hip ratio may carry information relevant to disease endpoints independently of waist girth or body mass index (10), waist circumference correlates better with visceral fat deposits as measured by computerized tomography (11). Defining adiposity as waist girth ≥ 94 cm has been proposed by experts in the European Group for the Study of Insulin Resistance (EGIR) (9). Furthermore, the euglycemic hyperinsulinemic clamp is not practical for epidemiologic research. The EGIR recommended use of fasting insulin levels to estimate insulin resistance and impaired fasting glycemia as a substitute for impaired glucose tolerance in epidemiologic studies (9). The EGIR also proposed lower cutoffs for hypertension ($\geq 140/90$ mmHg) that are in accordance with current WHO–International Society of Hypertension and Sixth Joint National Committee recommendations (9, 12, 13).

The NCEP Expert Panel also recently published a definition of the metabolic syndrome for clinical use (5). The metabolic syndrome was defined as three or more of the following: fasting plasma glucose levels ≥ 6.1 mmol/liter, serum triglycerides ≥ 1.7 mmol/liter, serum HDL cholesterol < 1.0 mmol/liter, blood pressure $\geq 130/85$ mmHg, and waist girth > 102 cm. Use of waist circumference > 94 cm was suggested for some men who might be genetically susceptible to insulin resistance (5).

Knowledge of the risk of developing type 2 diabetes associated with the metabolic syndrome as defined by the WHO or NCEP is scanty. Although type 2 diabetes is a heterogeneous disease, most type 2 diabetes patients are insulin resistant and also have the metabolic syndrome before onset of type 2 diabetes (1, 2, 14). Application of definitions to predicting diabetes in prospective cohort studies can serve to validate definitions of the metabolic syndrome. We compared the sensitivity, specificity, and prevalent and incident diabetes risk of definitions of the metabolic syndrome based on the WHO consultation (4) and NCEP (5) recommendations in a cohort of middle-aged nondiabetic men who

were followed for 4 years. The two modified WHO definitions (waist vs. waist-hip ratio) and the two NCEP definitions (waist > 102 cm vs. waist > 94 cm) differed only with regard to adiposity.

MATERIALS AND METHODS

The study population for the prospective, population-based Kuopio Ischemic Heart Disease Risk Factor Study (15) was a random, age-stratified sample of men living in eastern Finland aged 42, 48, 54, or 60 years at baseline. The University of Kuopio Research Ethics Committee approved the study. All subjects gave their written informed consent.

The Kuopio Ischemic Heart Disease Risk Factor Study 4-year follow-up study included 1,038 subjects who had undergone carotid ultrasound examination during the original study. Baseline visits were conducted between 1988 and 1989 and follow-up visits between 1992 and 1993. Both the baseline and the 4-year follow-up studies have been described in detail previously (15, 16).

For the present study, analyses were limited to the 1,005 men participating in the 4-year follow-up for whom complete data for assessment of the metabolic syndrome were available. Men who had diabetes at baseline ($n = 47$) were excluded from prospective analyses. Diabetes at baseline and at the 4-year follow-up was defined as fasting blood glucose ≥ 6.1 mmol/liter or a clinical diagnosis of diabetes with either dietary, oral, or insulin treatment (4, 17); impaired fasting glycemia was defined as fasting blood glucose of 5.6–6.0 mmol/liter (4).

Measurements of adiposity

Body mass index was computed as the ratio of weight (kg) to the square of height (m) (kg/m²). Waist circumference was defined as the average of two measurements taken after subject inspiration and after expiration (mean difference between the two measurements, ≤ 1.5 cm) at the midpoint between the lowest rib and the iliac crest. Waist-hip ratio was defined as the ratio of waist girth to the circumference of the hips measured at the trochanter major.

Blood pressure

Study subjects' blood pressure was measured with a random zero mercury sphygmomanometer (Hawksley & Sons, Ltd.; Lancing, United Kingdom). The measurement protocol included, after a supine rest of 5 minutes, three measurements in the supine position, one in the standing position, and two in the sitting position at 5-minute intervals. The mean of all six measurements was used as the systolic and diastolic blood pressures.

Biochemical determinations

Subjects were asked to fast for 12 hours before blood sampling. They were also asked to refrain from smoking for 12 hours and from consuming alcohol for 3 days before blood draws.

Blood glucose was measured at baseline and 4-year follow-up by using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. The serum samples for insulin determination were stored at -80°C . Serum insulin was determined by using a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark).

Fractions of low density lipoprotein and HDL cholesterol were separated from fresh serum by combined ultracentrifugation and precipitation. The cholesterol contents of lipoprotein fractions and serum triglycerides were measured enzymatically.

Metabolic syndrome

For men, the metabolic syndrome according to the WHO definition was modified for epidemiologic studies in part as proposed by the EGIR (9) and was defined as hyperinsulinemia (fasting insulin levels in the top 25 percent of the nondiabetic population), impaired fasting glycemia or diabetes, and the presence of at least two of the following: abdominal obesity, dyslipidemia (triglycerides ≥ 1.70 or HDL cholesterol < 0.9 mmol/liter), or hypertension (blood pressure $\geq 140/90$ mmHg or blood pressure medication use) (4). Insulin resistance was estimated as hyperinsulinemia based on fasting insulin concentrations in the upper 25 percent (9). Insulin resistance was also estimated as the bottom 25 percent of insulin sensitivity as measured by a recently validated index (quantitative insulin sensitivity check index (QUICKI)) based on fasting insulin and glucose concentrations ($[\log(\text{insulin}) + \log(\text{glucose})]^{-1}$) (18). Hypertension was defined according to the EGIR recommendations at a lower level than specified by the original WHO definition for consistency with current WHO–International Society of Hypertension and Sixth Joint National Committee recommendations (9, 12, 13). Microalbuminuria was not included in the definition (9). Abdominal obesity was defined on the basis of two definitions—1) according to the original WHO definition: waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m² (4), and 2) modified according to the EGIR recommendation: waist circumference ≥ 94 cm (9).

The metabolic syndrome as defined by the NCEP included three or more of the following: fasting plasma glucose levels ≥ 6.1 mmol/liter (blood glucose levels ≥ 5.6 mmol/liter), serum triglycerides ≥ 1.7 mmol/liter, serum HDL cholesterol < 1.0 mmol/liter, blood pressure $\geq 130/85$ mmHg, and waist girth > 102 cm (5). Use of waist girth > 94 cm was suggested for men genetically susceptible to insulin resistance (5).

Inclusion of a measure of hyperglycemia in the definitions of the metabolic syndrome will obviously affect the prediction of diabetes. Therefore, we also repeated the analyses by excluding impaired fasting glycemia from the definitions.

Statistical analysis

Differences in baseline clinical and biochemical characteristics among men who had diabetes at baseline, who developed diabetes during follow-up, and who remained nondiabetic were tested for statistical significance with one-way analysis of variance and, where indicated, the chi-

square test. The association of the metabolic syndrome with the risk of developing diabetes was estimated by using logistic regression analysis, adjusting for age. Sensitivity and specificity of the definitions of the metabolic syndrome for prevalent and incident diabetes were calculated and then compared by using McNemar's test. Receiver operating characteristic analysis was performed by using continuous variables to derive cutoffs for waist circumference corresponding to body mass index ≥ 25 kg/m² and 30 kg/m². In this paper, data are presented as means and standard deviations, medians (interquartile ranges), or simple percentages. Triglyceride and insulin concentrations were corrected for skewing by log transformation but are presented here as medians (interquartile ranges) by using untransformed values. Significance was considered to be $p < 0.05$. All statistical analyses were performed with SPSS 10.0 software for Windows (SPSS, Inc., Chicago, Illinois).

RESULTS

Baseline

Compared with men who were nondiabetic throughout the study, men who had diabetes at baseline and men who developed diabetes during the 4-year follow-up were heavier and more dyslipidemic, hypertensive, and insulin resistant at baseline (table 1). The overwhelming majority who developed diabetes (88 percent) had a body mass index of ≥ 25 kg/m² (overweight or obese as defined by the National Institutes of Health and WHO (19, 20)), although most men who remained nondiabetic were also overweight. Most men who subsequently developed diabetes had a body mass index of < 30 kg/m², although more men who developed diabetes were obese.

Similarly, almost all men who developed diabetes had a waist-hip ratio of > 0.90 , although the majority of men who did not develop diabetes also had a waist-hip ratio of > 0.90 (table 1). Only 59 percent of men who developed diabetes had a waist circumference of ≥ 94 cm at baseline. Less than a third of the men who developed diabetes had a waist girth of > 102 cm.

Because the 94-cm and 102-cm waist circumference cutoffs were derived at least in part from a cross-sectional population study from the Netherlands in which those cutoffs corresponded to a body mass index of 25 kg/m² and 30 kg/m² (21), respectively, we repeated receiver operating characteristic analyses to derive cutoffs for this population. In this cohort, the body mass index cutoffs of ≥ 25 kg/m² and 30 kg/m² corresponded to a waist girth of ≥ 87 cm (sensitivity, 0.84; specificity, 0.84) and 96 cm (sensitivity, 0.86; specificity, 0.88), respectively. The cutoff of 87 cm was as sensitive as a body mass index of ≥ 25 kg/m² (0.90 vs. 0.88) in identifying men who developed diabetes during follow-up.

Association of the metabolic syndrome with development of diabetes

Men who met the WHO definition of the metabolic syndrome in which adiposity was defined as waist-hip ratio

TABLE 1. Baseline characteristics of the 47 middle-aged Finnish men who had diabetes mellitus at baseline, 51 who developed diabetes mellitus during a 4-year follow-up since the late 1980s, and 907 who were nondiabetic throughout the study*

	Prevalent diabetes mellitus at baseline (n = 47)	Incident diabetes mellitus at follow-up (n = 51)	No diabetes mellitus at baseline or follow-up (n = 907)	p value†
Age (years)	53.4 (5.8)	53.4 (5.8)	51.9 (6.7)	0.15
Smoker	27.7	36.8	33.9	0.60
Cardiovascular disease	38.3	43.1	34.3	0.39
Body mass index (kg/m ²)	28.2 (3.5)	29.6 (4.4)	26.5 (3.2)	<0.001
Waist girth (cm)	95.5 (11.3)	97.8 (11.3)	89.4 (9.0)	<0.001
Waist-hip ratio	0.98 (0.05)	0.97 (0.05)	0.94 (0.06)	<0.001
Blood pressure medication use	40.4	37.2	19.5	<0.001
Systolic blood pressure (mmHg)	140.6 (21.8)	136.9 (14.5)	131.3 (15.7)	<0.001
Diastolic blood pressure (mmHg)	88.6 (9.3)	91.9 (10.7)	87.2 (10.1)	0.004
Serum HDL‡ cholesterol (mmol/liter)	1.19 (0.28)	1.25 (0.27)	1.31 (0.30)	0.024
Serum triglycerides (mmol/liter)	1.63 (1.19, 2.78)	1.65 (1.11, 2.34)	1.17 (0.85, 1.69)	<0.001
Fasting blood glucose (mmol/liter)	7.71 (0.27)	5.24 (0.52)	4.50 (0.44)	<0.001
Impaired fasting glycemia	NA‡	35.3	1.8	<0.001
Fasting serum insulin (mU/liter)	16.4 (12.0, 21.3)	13.8 (8.5, 20.6)	9.1 (7.0, 11.9)	<0.001
Blood pressure ≥ 140/90 mmHg or medication use	66	80	54	<0.001
Blood pressure ≥ 130/85 mmHg or medication use	85	84	72	0.022
HDL cholesterol < 1.0	27	20	13	0.008
HDL cholesterol < 0.9	10.6	7.8	6.2	0.44
Triglycerides ≥ 1.7	49	49	25	<0.001
Adiposity (waist-hip ratio > 0.90)	87	90	72	0.001
Adiposity (waist girth > 102 cm)	21	31	8	<0.001
Adiposity (waist girth ≥ 94 cm)	57	59	30	<0.001
Adiposity (body mass index ≥ 25 kg/m ²)	83	88	65	<0.001

* Values are expressed as percentages, means (standard deviation), or medians (lower quartile, upper quartile).

† For the differences among groups (one-way analysis of variance).

‡ HDL, high density lipoprotein; NA, not applicable.

> 0.90 or body mass index ≥ 30 kg/m² had a nearly ninefold greater likelihood of developing diabetes than men without the metabolic syndrome (figure 1). Furthermore, sensitivity (0.83 and 0.67) and specificity (0.78–0.80) for detecting prevalent and incident diabetes, respectively, was quite high (table 2). Use of the insulin sensitivity index (QUICKI) to estimate insulin resistance resulted in a slightly higher sensitivity (0.69), specificity (0.82), and odds ratio (10.4) of the WHO definition for incident diabetes (not shown).

Men fulfilling the WHO definition of the metabolic syndrome in which adiposity was defined as waist girth ≥ 94 cm were 7.0 times more likely to develop diabetes during follow-up (figure 1). The metabolic syndrome definition of waist girth as ≥ 94 cm had a clearly lower sensitivity (0.68 and 0.57) for prevalent and incident diabetes, respectively, and was only slightly more specific (0.81–0.83) (table 2). We repeated the analyses by using the waist girth cutoff corresponding to a body mass index of ≥ 25 kg/m² in this population, 87 cm. The sensitivity, specificity, and odds ratio for the prediction of diabetes were virtually identical to the

WHO definition based on waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m² (not shown). Even when adiposity was defined as body mass index ≥ 25 kg/m² or waist ≥ 102 cm, a definition proposed by the National Institutes of Health for screening in the presence of other risk factors (20), results were nearly identical (not shown).

Use of the NCEP definition of the metabolic syndrome detected only 61 percent of prevalent and 41 percent of incident diabetes, although specificity was quite high (0.89–0.90) (table 2). The likelihood of men with the metabolic syndrome, as defined by the NCEP, to develop diabetes was high (figure 1).

Because the NCEP also pointed out that some genetically susceptible men with only mild increases in abdominal obesity (waist circumference, 94–102 cm) can develop multiple metabolic risk factors and should similarly benefit from intervention, we repeated the analyses by using waist circumference > 94 cm. Prevalence increased from 11 percent to 18 percent, with an odds ratio of 5.0 for developing diabetes during follow-up (figure 1). Sensitivity for

TABLE 2. Prevalence of the definitions of the metabolic syndrome and their sensitivity and specificity* for prevalent and incident cases of diabetes mellitus in middle-aged Finnish men followed for 4 years since the last 1980s

Metabolic syndrome definition	Prevalence of the metabolic syndrome (<i>n</i> = 1,005)		Prevalence of diabetes mellitus (<i>n</i> = 1,005)		Sensitivity†	Specificity‡
	No.	%	No.	%		
WHO, WHR ≥ 0.91	250	24.9	47	4.7	0.83	0.78
WHO, waist girth ≥ 94 cm	212	21.1	47	4.7	0.68	0.81
NCEP, waist girth > 102 cm	138	13.7	47	4.7	0.61	0.89
NCEP, waist girth > 94 cm	206	20.5	47	4.7	0.72	0.82
	Prevalence of the metabolic syndrome at baseline (<i>n</i> = 958)		Incidence of diabetes mellitus during follow-up (<i>n</i> = 958)			
	No.	%	No.	%		
WHO, WHR ≥ 0.91	211	22.0	51	5.3	0.67	0.80
WHO, waist girth ≥ 94 cm	180	18.8	51	5.3	0.57	0.83
NCEP, waist > 102 cm	109	11.4	51	5.3	0.41	0.90
NCEP, waist > 94 cm	167	18.0	51	5.3	0.49	0.84

* Statistical significance was calculated by using McNemar's test.

† Differences in sensitivity of the World Health Organization (WHO) definition with waist-hip ratio (WHR) > 0.90 vs. the WHO definition with waist girth ≥ 94 cm—at baseline, *p* = 0.016; at follow-up, *p* = 0.063 vs. the National Cholesterol Education Program (NCEP) definition with waist girth ≥ 102 cm—at baseline, *p* = 0.006; at follow-up, *p* < 0.001 vs. the NCEP definition with waist girth ≥ 94 cm—at baseline, *p* = 0.18; at follow-up, *p* = 0.022.

‡ Differences in specificity of the WHO definition with WHR > 0.90 vs. all other definitions at baseline and follow-up—*p* < 0.001.

prevalent (0.72) and incident (0.49) diabetes improved (table 2). Again, because a waist circumference of ≥87 cm corresponds to a body mass index of ≥25 kg/m² in this population,

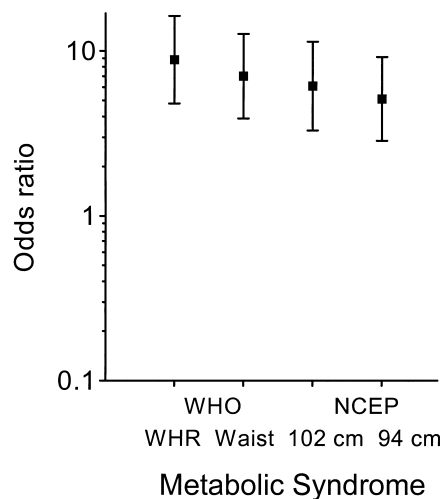


FIGURE 1. Age-adjusted log odds ratios and 95% confidence intervals for the development of diabetes in middle-aged Finnish men followed for 4 years since the late 1980s, as predicted by four definitions of the metabolic syndrome: 1) a modified World Health Organization (WHO) definition in which adiposity was defined as waist-hip ratio (WHR) > 0.90 or body mass index ≥ 30 kg/m² (WHO WHR), 2) a modified WHO definition in which abdominal obesity was defined as waist girth ≥ 94 cm (WHO Waist), 3) the National Cholesterol Education Program (NCEP) definition in which abdominal obesity was defined as waist circumference > 102 cm (NCEP 102 cm), and 4) the NCEP definition in which abdominal obesity was defined as waist girth > 94 cm (NCEP 94 cm).

we repeated the analyses by using a waist girth of ≥87 cm. Prevalence increased to 23 percent, and, with waist as 87 cm, the sensitivity, specificity, and odds ratio for predicting diabetes were 0.59, 0.79, and 5.1, respectively (not shown).

In corresponding analyses in which impaired fasting glycemia was excluded from the definitions, sensitivity, especially for the NCEP definitions, decreased (WHO definition with waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m², and sensitivity, 0.55; WHO definition with waist ≥ 94 cm and sensitivity, 0.49; NCEP definition with waist > 102 cm and sensitivity, 0.31; and NCEP definition with waist > 94 cm and sensitivity, 0.37), with almost no effect of specificity (not shown).

Clustering of insulin resistance and components of the metabolic syndrome

Over 95 percent of men with the metabolic syndrome as defined by the WHO had hyperinsulinemia. Conversely, over 80 percent of the men with insulin resistance had the metabolic syndrome with adiposity as defined by the WHO, emphasizing the clustering of insulin resistance and other components of the metabolic syndrome. At baseline, 11 percent of men had the metabolic syndrome according to both the NCEP definition using the lower 94-cm cutoff for waist circumference and the WHO definition based on waist-hip ratio > 0.90, of whom 23 (21 percent) developed diabetes.

DISCUSSION

The WHO definition of the metabolic syndrome that included waist-hip ratio > 0.90 or body mass index ≥ 30 kg/

m² was the most sensitive of the definitions for diabetes, detecting over four fifths of prevalent and two thirds of incident cases of diabetes with good specificity (0.78–0.80). The NCEP definition in which adiposity was defined as waist girth > 102 cm missed most incident cases of diabetes, although it was the most specific. All four definitions identified subjects at high risk for developing diabetes during follow-up in this population-based cohort of middle-aged men.

The WHO definition of the metabolic syndrome used in this study was modified largely according to the EGIR recommendations (9). The original WHO definition included insulin resistance as measured by the euglycemic hyperinsulinemic clamp and impaired glucose tolerance (4). At the same time, the WHO consultation acknowledged the need for internationally agreed-upon criteria for insulin resistance and hyperinsulinemia. Clamp studies are not well suited to most epidemiologic research, and, for many studies, glucose tolerance tests are not possible. Our study suggests that the EGIR recommendation to estimate insulin resistance by using hyperinsulinemia instead of clamp studies and to use impaired fasting glycemia instead of impaired glucose tolerance to define the metabolic syndrome is valid for epidemiologic studies. The recently validated insulin sensitivity index QUICKI, closely related to homeostasis model assessment (HOMA) (18), slightly increased the sensitivity and specificity for prevalent and incident diabetes. Hypertension was defined according to the EGIR recommendations at a lower level ($\geq 140/90$ mmHg) than the original WHO definition ($\geq 160/90$ mmHg) for consistency with current WHO–International Society of Hypertension and Sixth Joint National Committee recommendations (9, 12, 13). In addition, as recommended by the EGIR (9), microalbuminuria was not included in the definition. The EGIR also recommended that triglycerides ≥ 2.0 or HDL cholesterol < 1.0 mmol/liter be used to define dyslipidemia (9). A triglyceride cutoff of ≥ 1.70 mmol/liter has been recommended by both the WHO and NCEP. Definitions of the metabolic syndrome using this cutoff are slightly more sensitive for predicting diabetes than those using triglycerides ≥ 2.0 . HDL cholesterol cutoffs of 0.9 mmol/liter versus 1.0 mmol/liter have little effect on the prevalence of the metabolic syndrome or its sensitivity or specificity for diabetes. We therefore used the original WHO definition of dyslipidemia.

One of the most controversial aspects of the metabolic syndrome is the definition of adiposity. The WHO definition in which adiposity was defined by waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m² detected diabetes well, identifying 83 percent of prevalent and 67 percent of incident cases of diabetes, with a specificity of 0.78–0.80. The WHO definition in which adiposity was modified according to the EGIR recommendation as waist circumference ≥ 94 cm performed less well, present at baseline in only 68 percent of prevalent and 57 percent of incident cases of diabetes. The NCEP definition in which adiposity was defined as waist circumference > 102 cm was quite specific but insensitive, detecting only 61 percent of prevalent and 41 percent of incident diabetes. The NCEP recommendations suggest that some men may be genetically predisposed to the metabolic

syndrome even at lower levels of abdominal obesity, with waist circumferences of 94–102 cm (5). Using a cutoff of 94 cm for waist girth improved sensitivity of the definition to 0.72 for prevalent and 0.49 for incident diabetes with decreased, but still good specificity (0.82–0.84). This finding suggests that the genetic susceptibility for the metabolic syndrome associated with waist circumferences of 94–102 cm could be generalized to all middle-aged men, at least in the Finnish population.

The 94-cm and 102-cm cutoffs for waist circumference are influenced by a Netherlands cross-sectional study in which these cutoffs corresponded to body mass indexes of ≥ 25 kg/m² and ≥ 30 kg/m², respectively (21). A waist girth cutoff of 87 cm corresponded to a body mass index of ≥ 25 kg/m² in the nondiabetic Kuopio Ischemic Heart Disease Risk Factor Study cohort, underscoring the well-described (19) variable and population-specific relation of waist circumference to body mass index, even in northern European populations. Substituting a waist girth cutoff of 87 cm improved sensitivity of the NCEP definition to 0.59 for new-onset diabetes, with decreased, but still quite high specificity (0.79). Similarly, defining adiposity as waist girth ≥ 87 cm or even as body mass index ≥ 25 kg/m² or waist girth ≥ 102 cm (action level in the presence of other risk factors, as recommended by the National Institutes of Health) for the modified WHO definition of the metabolic syndrome was more sensitive than defining adiposity as waist ≥ 94 cm and as sensitive as defining adiposity as waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m² in detecting prevalent and incident diabetes.

Even mild overweight, especially in the presence of insulin resistance, increases the risk of diabetes (19, 22). Both the WHO and NCEP definitions of the metabolic syndrome are based on insulin resistance, the WHO definition directly and the NCEP definition indirectly through markers or correlates of insulin resistance. Failure to consider even mild overweight or abdominal obesity in the presence of insulin resistance or markers of insulin resistance as a significant risk factor could be a major shortcoming from both a clinical and public health perspective, missing most persons at risk for developing an increasingly common disease such as diabetes, which is associated with high morbidity and mortality.

Even though mild disturbances in glucose metabolism are a central feature of the metabolic syndrome, including a measure of hyperglycemia in the definitions is problematic when diabetes is used as an endpoint. Even when impaired fasting glycemia was excluded from the definitions, the sensitivity of the WHO definitions was still fairly high (0.49–0.55), whereas the sensitivity of the NCEP definitions was only 0.31–0.37. The relatively greater effect of removing hyperglycemia from the NCEP definitions is mainly due to the absence of a measure of insulin resistance (e.g., hyperinsulinemia). Excluding hyperglycemia from the definitions did not affect specificity.

The WHO definition of the metabolic syndrome based on waist-hip ratio > 0.90 or body mass index ≥ 30 kg/m² was common, present in slightly more than one fifth of all nondiabetic men at baseline. Over 95 percent of men who had the metabolic syndrome had hyperinsulinemia. Conversely,

over 80 percent of the men with insulin resistance had the metabolic syndrome with adiposity as defined by the WHO, emphasizing the clustering of insulin resistance and other components of the metabolic syndrome. The metabolic syndrome that included the EGIR definition of adiposity (waist \geq 94 cm) was less prevalent, affecting about 19 percent of the men at baseline. The NCEP definition in which adiposity was defined as waist $>$ 102 cm was much less common, present in about 11 percent of the men at baseline. Using a cutoff of 94 cm for waist girth increased prevalence to 18 percent.

At baseline, 11 percent of the men had the metabolic syndrome according to both the NCEP definition in which the lower 94-cm cutoff for waist circumference was used and the WHO definition based on waist-hip ratio $>$ 0.90; 23 (21 percent) of these men developed diabetes. This concurrence occurred even though the WHO and NCEP used rather different approaches to define the metabolic syndrome (the former based strongly on insulin resistance and the latter on only the numbers of features related to insulin resistance), again emphasizing clustering of components of the metabolic syndrome. Despite the concurrence of the WHO and NCEP definitions, the absence of a measure of insulin resistance (e.g., hyperinsulinemia) in the definition may also partly explain the lower sensitivity of the NCEP definitions in detecting prevalent and incident diabetes.

An obvious shortcoming of using type 2 diabetes as an endpoint for evaluating the sensitivity of the metabolic syndrome is that few data are available on the proportion of type 2 diabetes cases expected to have the metabolic syndrome prior to developing diabetes. Even so, type 2 diabetes is closely related to the metabolic syndrome and can in large part be considered an end-stage manifestation of this syndrome. Therefore, definitions of the metabolic syndrome can be compared according to their sensitivity and specificity for detecting new cases of incident diabetes in a prospective cohort study design. Roughly 5–10 percent of middle-aged diabetic patients have latent autoimmune diabetes of the adult (23), in which insulin secretion is the primary defect, and the overall proportion of diabetic patients thought to have insulin resistance before onset of diabetes has been estimated to be 75–85 percent (14, 24). If this information were taken into account, the sensitivity of the WHO and NCEP definitions in detecting prevalent and incident diabetes in which the metabolic syndrome may be expected to precede diagnosis would be even higher.

The WHO and NCEP definitions of the metabolic syndrome appear valid, identifying those with a five- to nine-fold increased likelihood of developing diabetes during follow-up in this population-based cohort of middle-aged men. The modified WHO definition based on waist-hip ratio $>$ 0.90 was the most sensitive in detecting prevalent and incident diabetes and had good specificity. The NCEP definition in which adiposity was defined as waist girth $>$ 102 cm was the most specific, but it did not detect most cases of incident diabetes. Defining adiposity as waist circumference $>$ 94 cm improves the sensitivity of the NCEP definition.

ACKNOWLEDGMENTS

The Kuopio Ischemic Heart Disease Risk Factor Study was supported by the Academy of Finland (grants for projects 41471, 1041086, and 2041022 to Dr. Jukka T. Salonen); the Ministry of Education of Finland; and the National Heart, Lung and Blood Institute (grant HL44199 to Dr. George A. Kaplan).

Timo Lakka was a postdoctoral researcher of the Academy of Finland.

The authors are indebted to Dr. Kristiina Nyysönen and Kari Seppänen for supervising chemical analyses and to Dr. Riitta Salonen for participation in the management of data collection.

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