Cardiovascular Morbidity and Mortality Associated With the Metabolic Syndrome

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OBJECTIVE — To estimate the prevalence of and the cardiovascular risk associated with the metabolic syndrome using the new definition proposed by the World Health Organization (WHO).

RESEARCH DESIGN AND METHODS — A total of 4,483 subjects aged 35–70 years participating in a large family study of type 2 diabetes in Finland and Sweden (the Botnia study) were included in the analysis of cardiovascular risk associated with the metabolic syndrome. In subjects who had type 2 diabetes (n = 1,697), impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) (n = 798), or insulin-resistance with normal glucose tolerance (NGT) (n = 1,988), the metabolic syndrome was defined as presence of at least two of the following risk factors: obesity, hypertension, dyslipidemia, or microalbuminuria. Cardiovascular mortality was assessed in 3,606 subjects with a median follow-up of 6.9 years.

RESULTS — In women and men, respectively, the metabolic syndrome was seen in 10 and 15% of subjects with NGT, 42 and 64% of those with IFG/IGT, and 78 and 84% of those with type 2 diabetes. The risk for coronary heart disease and stroke was increased threefold in subjects with the syndrome ($P < 0.001$). Cardiovascular mortality was markedly increased in subjects with the metabolic syndrome (12.0 vs. 2.2%, $P < 0.001$). Of the individual components of the metabolic syndrome, microalbuminuria conferred the strongest risk of cardiovascular death (RR 2.80; $P = 0.002$).

CONCLUSIONS — The WHO definition of the metabolic syndrome identifies subjects with increased cardiovascular morbidity and mortality and offers a tool for comparison of results from different studies.

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In 1988, Gerald Reaven reintroduced the concept of syndrome X for the clustering of cardiovascular risk factors like hypertension, glucose intolerance, high triglycerides, and low HDL cholesterol concentrations (1). The syndrome is, however, much older, having been already observed in 1923 by Kylin, who described the clustering of hypertension, hyperglycemia, and gout as a syndrome (2). Subsequently, several other metabolic abnormalities have been associated with this syndrome, including obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation (3–6). The syndrome has also been given several other names, including the metabolic syndrome, the insulin resistance syndrome, the plurimetabolic syndrome, and the deadly quartet (7–11). The name "insulin resistance syndrome" has been widely used and refers to insulin resistance as a common denominator of the syndrome (12–14). The prevalence of the metabolic syndrome has varied markedly between different studies, most likely because of the lack of accepted criteria for the definition of the syndrome (15–16). In 1998, WHO proposed a unifying definition for the syndrome and chose to call it the metabolic syndrome rather than the insulin resistance syndrome (17). This name was chosen primarily because it was not considered established that insulin resistance was the cause of all the components of the syndrome.

A unifying definition would allow us to assess whether the clustering of risk factors is associated with an increased risk of cardiovascular disease in addition to the risk associated with the individual components. Thus, the aim of the current study was to assess the prevalence of and cardiovascular morbidity and mortality associated with the metabolic syndrome by applying the WHO definition in a high-risk Scandinavian population.

RESEARCH DESIGN AND METHODS

The Botnia study represents a large family study in Finland and Sweden that was initiated in 1990 with the aim of identifying early metabolic defects in families with type 2 diabetes (18). From a total of 6,645 individuals participating in the Botnia study, all subjects aged 35–70 years (n = 4,483) were included in the present study. Patients with antibodies to GAD (GADAbs) (19) and patients with maturity-onset diabetes of the young, verified by DNA analysis (20), were excluded.

Glucose tolerance was assessed according to the new American Diabetes Association/WHO criteria using a 75-g oral glucose tolerance test (OGTT) (17). Thus, subjects with a fasting plasma glucose ≥7.0 mmol/l and/or a 2-h plasma glucose ≥11.1 mmol/l during an OGTT were considered to have diabetes (n = 1,697),

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Abbreviations: AER, albumin excretion rate; CHD, coronary heart disease; CV, coefficient of variation; ECG, electrocardiogram; GADAb, antibody to GAD; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MI, myocardial infarction; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization; WHR, waist-to-hip ratio.

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

and subjects with a fasting plasma glucose 6.1–6.9 mmol/l and/or a 2-h plasma glucose 7.8–11.0 mmol/l were considered to have abnormal glucose tolerance, which included both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) ($n = 798$). Furthermore, 1,988 subjects had normal glucose tolerance (NGT), i.e., fasting plasma glucose <6.1 mmol/l and 2-h glucose <7.8 mmol/l.

Total and cardiovascular mortality was assessed in 3,606 subjects from the original Botnia centers in western Finland, with a median follow-up of 6.9 years. Mortality data were obtained from a central death-certificate registry. During this period, 360 individuals had died. Cardiovascular mortality was classified using the 9th revision of the International Classification of Diseases (cardiovascular diagnosis codes 390–459) before 1997 and the 10th revision (codes I 00–I 99) thereafter.

Table 1—*Clinical and metabolic characteristics in 35–70-year-old subjects with NGT, IFG/IGT, and diabetic (type 2) glucose tolerance*

	NGT	IFG/IGT	Type 2 diabetes
n (F/M)	1,988 (1133/855)	798 (397/401)	1,697 (804/893)
Age (years)	50.5 ± 9.7	53.5 ± 10.0	58.6 ± 8.5
BMI (kg/m^2)	25.9 ± 3.7	27.3 ± 4.4	29.5 ± 4.9
WHR			
Men	0.95 ± 0.06	0.96 ± 0.06	0.99 ± 0.06
Women	0.83 ± 0.07	0.84 ± 0.08	0.90 ± 0.07
Fasting plasma glucose (mmol/l)	5.4 ± 0.5	6.1 ± 0.6	9.8 ± 3.3
HbA_{1c} (%)	5.3 ± 0.6	5.4 ± 0.6	7.5 ± 1.8
Fasting insulin (mU/l)*	7.5 ± 4.5	10.4 ± 6.0	15.2 ± 11.2
$HOMA_{IR}$*	1.80 ± 1.13	2.83 ± 1.69	6.58 ± 5.87
Cholesterol (mmol/l)	5.7 ± 1.1	5.8 ± 1.1	5.8 ± 1.1
HDL cholesterol (mmol/l)	1.38 ± 0.36	1.27 ± 0.32	1.15 ± 0.3
Triglycericdes (mmol/l)	1.29 ± 0.80	1.58 ± 0.86	2.08 ± 1.60
LDL cholesterol (mmol/l)	3.77 ± 1.00	3.88 ± 0.99	3.78 ± 0.97
Lipid-lowering medication	0.5	1.4	1.7
Antihypertensive treatment	15.5	21.9	46.3
Systolic blood pressure†	126.3 ± 16.2	132.8 ± 16.6	137.2 ± 17.0
Diastolic blood pressure†	77.9 ± 9.5	79.9 ± 9.5	80.5 ± 9.8
History of MI			
Men	3.2	7.1	13.4
Women	1.0	1.3	5.8
Previous stroke	1.3	2.3	5.2
Current smoking			
Men	23	17	16
Women	12	12	11

Data are means ± SD and %, unless otherwise indicated. *Insulin-treated patients excluded; †only untreated patients.

Methods

Fasting blood samples were drawn for the measurement of HbA_{1c}, total cholesterol, HDL cholesterol, and triglyceride concentrations.

An OGTT was performed in all subjects with fasting plasma glucose <11 mmol/l who were not treated with insulin. Samples for the measurements of blood glucose and serum insulin were drawn at –10, 0, 30, 60, and 120 min during the OGTT. Urine for the measurement of albumin excretion rate (AER) was collected either during the OGTT ($n = 1,082$) or overnight ($n = 1,579$). AER measured overnight correlated with AER during OGTT ($r = 0.605$, $P < 0.001$; $n = 442$). BMI was calculated after body weight and height were measured with subjects in light clothing without shoes. Waist circumference was measured with a soft tape on standing subjects midway between the lowest rib and the iliac crest. Hip circumference was measured over the widest part of the gluteal region, and the waist-to-hip ratio (WHR) was calculated as a measure of central obesity. Two blood pressure recordings were obtained from the right arm of patients in a sitting position after 30 min of rest at 5-min intervals, and their mean value was calculated.

A standardized health questionnaire was completed by specially-trained nurses, covering the subjects' past medical history, including current and previous medication, information about other diseases (particularly hypertension, coronary heart disease [CHD], myocardial infarction [MI], and stroke), smoking habits, alcohol consumption, physical activity, and family history of diabetes and cardiovascular diseases. CHD was defined as using nitroglycerine, experiencing typical chest pain, or having a history of previous MI. This information was validated against electrocardiogram (ECG) changes (Minnesota codes 1.1-3, 4.1-4, 5.1-3) compatible with ischemic heart disease (21) in all subjects from one of the centers ($n = 555$). MI, defined in accordance with the WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) criteria (22), and stroke (including both ischemic and hemorrhagic stroke) were defined as events requiring hospitalization; this information was verified from local hospital records.

To obtain an estimate of insulin resistance, we applied the homeostasis model assessment of insulin resistance ($HOMA_{IR}$) using the following formula: $HOMA_{IR}$ = fasting insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (23). $HOMA_{IR}$ was not estimated in patients treated with insulin.

Assays

Plasma glucose was measured with a glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Serum insulin concentrations were measured with radioimmunoassay (Pharmacia & Upjohn, Uppsala, Sweden) with an interassay coefficient of variation (CV) of 5%. Urine albumin concentrations were measured by an immunoturbidimetric method, with an interassay CV of 7.5%. Serum total cholesterol, HDL cholesterol, and triglycerides were measured on a Cobas Mira analyzer (Hoffman LaRoche, Basel, Switzerland). LDL cholesterol concentrations were calculated using the Friedewald formula (24). GADAbs were determined by a modified radiobinding assay using ^{35}S-labeled recombinant human GAD_{65} (19). HbA_{1c} concentrations were measured by high-pressure liquid chromatography (Diamat, Hercules, CA) with a reference range of 4–6%.

Table 2—*Prevalence of the metabolic syndrome and the different components of the metabolic syndrome* in male and female subjects of different age decades with NGT, abnormal IFG/IGT, and diabetic glucose tolerance*

	NGT		IFG/IGT		Type 2 diabetes†	
	Male	Female	Male	Female	Male	Female
Metablic syndrome						
all 35–70 years	15	10	64	42	84	78
40–49 years	12	6	59	38	87	78
50–59 years	20	9	67	44	83	74
60–69 years	20‡	19‖	66	52‡	84	81
Obesity						
all 35–70 years	76	36	86	51	92	78
40–49 years	76	34	87	49	95	80
50–59 years	81	32	86	56	93	79
60–69 years	80	44‡	89	53	92	78
Dyslipidemia						
all 35–70 years	29	16	45	31	54	56
40–49 years	31	13	51	25	66	64
50–59 years	28	17	46	31	55	51
60–69 years	23	21‡	39	37‡	50§	57
Hypertension						
all 35–70 years	23	24	31	35	55	59
40–49 years	20	17	19	31	42	47
50–59 years	27	29	41	34	55	53
60–69 years	35‖	41‖	39§	47‡	59§	67‖
Microalbuminuria						
all 35–70 years	4	3	7	6	22	12
40–49 years	3	4	1	6	14	18
50–59 years	3	2	8	8	19	12
60–69 years	8	1	9‡	9	26	11
Insulin resistance¶						
all 35–70 years	25	25	58	59	87	89
40–49 years	23	19	53	52	87	89
50–59 years	28	24	65	57	87	89
60–69 years	29	35‖	59	68‡	86	90

Data are %. *The definition of the metabolic syndrome was based on the recent WHO proposal (17); †$P <$ 0.001 for differences in all variables between subjects with diabetes and NGT/IFG/IGT when men and women aged 35–70 years were compared separately; ‡$P < 0.05$; §$P < 0.01$; ‖$P < 0.001$ when age decade 60–69 was compared to age decade 40–49; ¶highest quartile of $HOMA_{IR}$.

Definition of the metabolic syndrome

In accordance with the WHO proposal, the components of the metabolic syndrome are: *1*) hypertension, defined as antihypertensive treatment and/or elevated blood pressure (>160 mmHg systolic or >90 mmHg diastolic); *2*) dyslipidemia, defined as elevated plasma triglyceride (≥1.7 mmol/l) and/or low HDL cholesterol (<0.9 mmol/l in men, <1.0 mmol/l in women) concentrations; *3*) obesity, defined as a high BMI (≥30 kg/m^2) and/or a high WHR ratio (>0.90 in men, >0.85 in women); and *4*) microalbuminuria (urinary AER ≥ 20 μg/min). A person with type 2 diabetes or IFG/IGT has the metabolic syndrome if two of the criteria listed above are fulfilled. A person with NGT has the metabolic syndrome if he/she fulfils two of the criteria in addition to being insulin resistant. Insulin resistance is defined as the highest quartile of the $HOMA_{IR}$ index (17).

Statistical methods

The values are given as means ± SD. The group frequencies were compared by χ^2 or Fisher's exact tests. Spearman rank correlations were used to demonstrate relationships between variables. A multiple regression analysis was carried out with CHD, previous MI, or stroke as dependent variables and age, sex, and the metabolic syndrome or its components as independent variables. In the multiple regression analysis assessing risk factors for cardiovascular mortality, LDL-cholesterol and current smoking were also included as independent variables. In the multiple regression analysis, LDL-cholesterol and age were used as continuous variables, and the other variables were used as categorical variables. The statistical analyses were performed with an SPSS program for Windows. A P value <0.05 was considered statistically significant.

RESULTS — The clinical and metabolic characteristics of subjects with various degrees of glucose tolerance are given in Table 1. Patients with type 2 diabetes were older and had higher BMI than the other groups. They also reported the highest prevalence of MI and stroke.

Table 2 shows the prevalence of the different components of the metabolic syndrome in relation to glucose tolerance, sex, and age decades. The prevalence of

Table 3—*Prevalence of different combinations of the individual components of the metabolic syndrome* in 35–70-year-old male and female subjects with NGT, IFG/IGT, and diabetic glucose tolerance*

	NGT		IFG/IGT		Type 2 diabetes	
	Male	Female	Male	Female	Male	Female
Obesity + dyslipidemia	25	9	41	21	51	49
Obesity + hypertension	20	11	28	23	50	50
Obesity + hypertension + dyslipidemia	7	3	15	10	29	31
Hypertension + dyslipidemia	8	5	16	14	31	36
Obesity + microalbuminuria	3	2	6	3	21	11
Hypertension + microabluminuria	2	2	3	3	16	10
Dyslipidemia + microabluminuria	1	1	4	2	14	9

Data are %. *The definition of the metabolic syndrome was based on the recent WHO proposal (17).

Table 4—*Prevalence and RR of CHD*, MI, and stroke in relation to the presence of the metabolic syndrome†*

	Metabolic syndrome			
	Yes	No	RR‡	*P*‡
NGT (n = 1,808)				
CHD	9.2	4.1	1.73 (1.01–2.95)	0.04
Previous MI	3.1	1.6	1.24 (0.52–2.97)	0.62
Previous stroke	2.2	1.6	1.31 (0.48–3.62)	0.59
IFG/IGT (n = 685)				
CHD	11.0	5.3	1.82 (0.98–3.38)	0.06
Previous MI	5.8	2.2	2.03 (0.81–5.08)	0.13
Previous stroke	3.6	0.9	3.64 (1.01–13.13)	0.05
Type 2 DM (n = 1,430)				
CHD	27.1	13.5	2.23 (1.52–3.26)	<0.001
Previous MI	11.2	4.7	2.26 (1.25–4.10)	0.007
Previous stroke	5.7	2.9	1.79 (0.85–3.79)	0.13
All subjects (n = 3,928)				
CHD	21.4	5.5	2.96 (2.36–3.72)	<0.001
Previous MI	9.0	2.1	2.63 (1.86–3.72)	<0.001
Previous stroke	4.8	1.4	2.27 (1.47–3.50)	<0.001

Data are % and RR (95% CI). *Defined as typical chestpain/use of nitroglycerine/previous MI; †definition of the syndrome was based on the recent WHO proposal (17); ‡adjusted for age and sex.

obesity was high in all groups, and it was especially high in male subjects; 76% of men with NGT and 92% of diabetic men fulfilled the criteria of obesity.

The prevalence of dyslipidemia and hypertension were both increased twofold in type 2 diabetic patients compared with subjects with NGT. The prevalence of microalbuminuria was low in subjects with NGT and IFG/IGT (3–7%), whereas 22% of the diabetic men and 12% of the diabetic women had microalbuminuria; in most subjects, it was associated with hypertension. Isolated microalbuminuria without hypertension was seen in only 6.8% of male and 2.3% female subjects with diabetes. There was a clear increase in the prevalence of the metabolic syndrome with increasing age (Table 2). Hypertension in particular increased significantly in the highest age decade.

The prevalence of insulin resistance, defined as the highest quartile of $HOMA_{IR}$, was increased twofold in subjects with IFG/IGT and threefold in patients with type 2 diabetes compared with subjects with NGT. In women with NGT, the prevalence of insulin resistance increased from 19% in the age decade of 40–49 years to 35% in the age decade of 60–69 years ($P < 0.001$).

The most common combination was obesity plus dyslipidemia or obesity plus hypertension; this was seen in ~10% of the subjects with NGT and ~50% of the patients with diabetes. The combination of obesity, dyslipidemia, and hypertension was seen in 3–7% of the subjects with NGT and in ~30% of the patients with type 2 diabetes (Table 3).

Using the proposed WHO criteria, the prevalence of the metabolic syndrome was more common in nondiabetic men than in women (64 and 42% in subjects with IFG/IGT and 15 and 10% in subjects with NGT, respectively). The sex-specific difference almost disappeared in the type 2 diabetic patients (84 and 78%, respectively) (Table 2). In women with NGT, the prevalence of the metabolic syndrome increased from 6% in the youngest age decade (40–49 years) to 19% in the oldest (60–69 years) ($P < 0.001$).

Prevalence of cardiovascular disease in relation to the metabolic syndrome. In all subjects, a history of CHD, MI, and stroke was more common in those with the metabolic syndrome than it was in those without the syndrome ($P < 0.001$) (Table 4). In particular, a history of CHD was more frequent in subjects with the metabolic syndrome than it was in those without the syndrome in the NGT (9.2 vs. 4.1%, $P = 0.04$) and the type 2 diabetes (27.1 vs. 13.5%, $P < 0.001$) groups, whereas the difference in subjects with IFG/IGT was of borderline statistical significance (11.0 vs. 5.3%; $P = 0.06$). In a subset of 555 patients in whom the presence of CHD could be based on Minnesota coding of the ECG (21) in addition to the clinical data, the prevalence of CHD was increased even further in patients with the metabolic syndrome (35 vs. 8%, $P < 0.001$). A history of MI was increased in type 2 diabetic patients with the metabolic syndrome compared with those without the syndrome (11.2 vs. 4.7%; $P = 0.007$). Similarly, a history of stroke was more common in IFG/IGT subjects with the syndrome than it was in those without the syndrome (3.6 vs. 0.9%; $P = 0.05$).

Cardiovascular risk in relation to the different components of the metabolic syndrome. Using a multiple regression analysis, we also analyzed the risk of cardiovascular disease in relation to the presence of the metabolic syndrome and the different components of the syndrome (Table 5). Age and male sex were related to CHD (RR 1.12, $P < 0.001$ for age; RR 1.44, $P = 0.001$ for male sex), MI (RR

Table 5—*Multiple logistic regression analysis with CHD, previous MI, or stroke as dependent variables and the metabolic syndrome and its components as independent variables in subjects with complete data*

	CHD (n = 2,401)		MI (n = 2,404)		Stroke (n = 2,395)	
Independent variables	RR	*P*	RR	*P*	RR	*P*
The metabolic syndrome*	2.96	<0.001	2.63	<0.001	2.27	<0.001
Obesity	1.44	0.07	1.31	0.43	1.26	0.59
Dyslipidemia	1.73	<0.001	1.71	0.01	1.30	0.40
Hypertension	1.57	0.002	1.31	0.22	1.34	0.34
Microalbuminuria	0.94	0.77	0.76	0.37	0.85	0.73
Insulin resistance†	1.53	0.01	2.02	0.009	1.39	0.36

Adjusted for age and sex. *The metabolic syndrome was defined based on the WHO proposal (17); †defined as highest quartile of HOMA.

Table 6—*Multiple logistic regression anaysis with CHD as a dependent variable and the presence of the metabolic syndrome* or its individual components as independent variables in subjects with complete data (n = 2,401)*

	NGT (n = 1,136)		IFG/IGT (n = 488)		Type 2 diabetes (n = 777)	
	RR	*P*	RR	*P*	RR	*P*
The metabolic syndrome*	1.73	0.04	1.82	0.06	2.23	<0.001
Obesity	1.15	0.68	1.79	0.26	1.48	0.20
Dyslipidemia	1.68	0.13	1.34	0.41	1.84	0.001
Hypertension	2.33	<0.001	1.08	0.82	1.31	0.16
Microabluminuria	0.65	0.59	0.59	0.44	0.94	0.81
Insulin resistance†	1.13	0.71	2.18	0.06	0.76	0.34

Adjusted for age and sex. *The metabolic syndrome was defined based on the recent WHO proposal (17); †defined as the highest quartile of HOMA.

1.11, $P < 0.001$; RR 3.18, $P < 0.001$), and stroke (RR 1.09, $P < 0.001$; RR 1.76, $P = 0.005$). Therefore, the data have been adjusted for age and sex. The presence of the syndrome was associated with an increased risk of CHD, MI, and stroke in all subjects (2.96, 2.63, and 2.27, respectively; $P < 0.001$), and this risk was greater than the risk associated with any of the individual components. Dyslipidemia was associated with an increased risk for CHD ($P < 0.001$), particularly among patients with type 2 diabetes (Table 6; RR 1.84; $P = 0.001$). Hypertension was associated with increased risk for CHD, particularly in subjects with NGT (RR 2.33; $P < 0.001$).

Total and cardiovascular mortality in relation to the metabolic syndrome. During the median follow-up of 6.9 years, 360 (10.0%) of the 3,606 patients had died, and of them, 209 (5.8%) died from cardiovascular disease. Compared with subjects without the metabolic syndrome, total mortality (18.0 vs. 4.6%, $P < 0.001$) and cardiovascular mortality (12.0 vs. 2.2%, $P < 0.001$) were increased in subjects with the syndrome. In a multiple regression analysis (Table 7) with cardiovascular mortality as the dependent variable and age, male sex, LDL cholesterol, and current smoking as independent variables, the RR of the metabolic syndrome was 1.81 ($P = 0.002$). When the metabolic syndrome was replaced by its components in the analysis, microalbuminuria was the strongest risk factor for cardiovascular death (RR 2.80, $P < 0.001$). A multiple logistic regression analysis with microalbuminuria as dependent factor clearly showed that except for obesity, all other components of the metabolic syndrome, including insulin resistance, were associated with microalbuminuria (not shown).

CONCLUSIONS — In the current study, we applied the criteria for the metabolic syndrome recently proposed by a WHO workgroup (17) to subjects with normal, impaired, and diabetic glucose tolerance. The metabolic syndrome was present in ~10% of subjects with NGT, ~50% of subjects with IFG/IGT, and ~80% of subjects with type 2 diabetes. It was more common in men than in women among subjects with NGT (15 vs. 10%) and IFG/IGT (64 vs. 42%), but not in patients with type 2 diabetes (84 vs. 78%). Importantly, the presence of the metabolic syndrome was associated with an increased risk for cardiovascular morbidity and mortality with an odds ratio of 3 for CHD and 1.8 for cardiovascular mortality. The CHD morbidity risk associated with the cluster of risk factors was greater than the risk associated with the individual components.

In previous studies, the prevalence of the metabolic syndrome has varied widely, primarily due to different definitions of the syndrome or selection of different subgroups (16). In a Finnish population-based study, a metabolic syndrome defined as clustering of dyslipidemia and insulin resistance (defined as abnormal glucose tolerance or fasting plasma insulin ≥13 mU/l) was present in 17% of nondiabetic men and 8% of women (25). In the ARIC study population, a combination of hypertension (blood pressure >140/90 mmHg and/or the use of antihypertensive treatment) and dyslipidemia (triglycerides >2.26 mmol/l and/or HDL <0.9 mmol/l in men and <1.2 in women) was observed in 10% of the subjects (26).

The prevalence of the metabolic syndrome and its components is strongly dependent on the definition of the different components of the syndrome. Obesity defined by a high WHR was clearly more common than obesity defined as BMI >30 kg/m^2 (not shown in table). Using the proposed limits for WHR of 0.9 in men and 0.85 in women, 76% of men and 36% of women with NGT would be considered abdominally obese, whereas the corresponding figures using only a BMI of >30 kg/m^2 would be 10 and 14%, respectively. A higher cutoff level for WHR (1.0 in male subjects and 0.9 in female subjects) would increase the RR of CHD associated with the syndrome in NGT subjects from 1.73 ($P = 0.04$) to 2.36 ($P = 0.002$), but it would have little influence on the risk in subjects with IFG/IGT and type 2 diabetes.

Because many of the components of the metabolic syndrome are associated with insulin resistance, it has been suggested that the syndrome should instead

Table 7—*Multiple logistic regression analysis with cardiovascular mortality as a dependent variable and the metabolic syndrome* or its components as independent variables*

	All subjects (209 deaths)		Diabetic patients (168 deaths)	
	RR (95% CI)	*P*	RR (95% CI)	*P*
The metabolic syndrome*	1.81 (1.24–2.65)	0.002	1.15 (0.68–1.94)	0.60
Obesity	1.10 (0.63–1.96)	0.76	0.87 (0.43–1.76)	0.70
Dyslipidemia	0.99 (0.63–1.58)	0.98	0.93 (0.54–1.61)	0.80
Hypertension	1.78 (1.09–2.91)	0.02	1.43 (0.76–2.68)	0.27
Microalbuminuria	2.80 (1.62–4.83)	<0.001	3.17 (1.70–5.91)	<0.001
Insulin resistance†	1.53 (0.88–2.64)	0.13	1.44 (0.56–3.71)	0.45

Adjusted for age, sex, LDL cholesterol, and current smoking. *The metabolic syndrome was defined based on the recent WHO proposal (17); †defined as highest quartile of $HOMA_{IR}$.

be called the insulin resistance syndrome (14). In the Bruneck Study (15), the prevalence of insulin resistance (defined as top quintile of $HOMA_{IR}$) was 66% in subjects with IGT and 84% in subjects with type 2 diabetes. The corresponding figure in the current study, using the top quartile of $HOMA_{IR}$, would be very similar (59% in IFG/IGT and 88% in type 2 diabetic patients). In a recent Finnish study, clustering of a high BMI, high triglycerides, low HDL cholesterol, and endogenous hyperinsulinemia predicted cardiovascular mortality in patients with type 2 diabetes (27).

Why is insulin resistance not then included as a component of the syndrome also in subjects with IFG/IGT and diabetes in the WHO proposal? There are several explanations for this. Because insulin resistance defined as the top quartile of HOMA is seen in ~90% of patients with type 2 diabetes, the prevalence of the metabolic syndrome would not change much if insulin resistance was included as a component in this group (from 84 to 73% and from 78 to 71% in male and female subjects, respectively). Secondly, much of the insulin resistance in type 2 diabetes may be secondary to elevated glucose (28) and free fatty acid levels (29–30), and it is not known whether the cardiovascular risk associated with secondary insulin resistance is the same as that associated with insulin resistance in the prediabetic state. Finally, probably the most important argument against including insulin resistance as a component of the syndrome in patients with type 2 diabetes is that it is very difficult to quantitate insulin resistance in a hyperglycemic subject.

The clinical importance of the metabolic syndrome is related to its putative impact on cardiovascular morbidity and mortality; in the present study, the prevalence of CHD, MI, and stroke were approximately threefold higher in subjects with the metabolic syndrome than it was in those without the syndrome. The following question arises: Do we need to call the clustering of risk factors a syndrome or should we only list the individual risk factors? The combination of obesity and hypertension or dyslipidemia was the most common risk factor combination in subjects with IFG/IGT and diabetes. However, given the high frequency of obesity in this population, it had little influence of the RR of CHD in subjects with NGT, IFG/IGT, and diabetes (1.15, 1.79, and 1.48, respectively). The combination of hypertension and dyslipidemia was the second most common risk factor combination in subjects with NGT (8 and 5% in male and female subjects, respectively), IFG/IGT (16 and 14%), and diabetes (31 and 36%), and thereby it had the greatest influence on the CHD risk associated with the syndrome. Whereas hypertension was strongly associated with CHD in the NGT group (RR 2.33; $P < 0.001$), dyslipidemia was strongly predictive of CHD in the patients with type 2 diabetes (RR 1.84; $P = 0.001$). Interestingly, in subjects with IFG/IGT, insulin resistance conferred the greatest risk of CHD (RR 2.18; $P = 0.06$). The criteria for dyslipidemia were more dependent on the presence of hypertriglyceridemia than of low HDL-cholesterol; this could present a problem in patients with type 2 diabetes, in whom elevated triglyceride levels may be secondary to hyperglycemia (31).

The inclusion of microalbuminuria as part of the metabolic syndrome has been questioned (14) because of its rarity and lack of association with insulin resistance in some studies (32–33). Despite this, microalbuminuria has been a strong predictor of cardiovascular morbidity and mortality in several studies (34–37), and in the current study, it was associated with a markedly increased risk of cardiovascular death (RR 2.80; $P < 0.001$). In the current study, a multiple logistic regression analysis with microalbuminuria as a dependent factor clearly showed that except for obesity, all other components of the syndrome, including insulin resistance, were associated with microalbuminuria (not shown in table). Microalbuminuria has also been related to increased transcapillary albumin leakage (38), suggesting that microalbuminuria represents a surrogate measure of endothelial dysfunction. Whether insulin resistance is involved in the pathogenesis of microalbuminuria may be less important than the fact that microalbuminuria indicates an advanced stage of cardiovascular disease and is thereby associated with high cardiovascular mortality.

We acknowledge some of the limitations of this study. The use of a nurse-administered questionnaire to assess the presence of cardiovascular disease obviously underestimates the true prevalence of cardiovascular events by only taking into account MIs and strokes requiring hospitalization. However, because the patients had been treated in the local hospitals, we also had access to their hospital records. The diagnosis of CHD was based on a history of typical chest pain or the use of nitroglycerine or a history of previous MI. In a subset of patients, we used ECG analysis in addition to the clinical data for the diagnosis of CHD. As expected, the prevalence of coronary heart disease increased in this subset, especially in subjects who fulfilled the criteria for the metabolic syndrome (35 vs. 8%), yielding a RR of 3.97 ($P < 0.001$, adjusted for age and sex) for the metabolic syndrome. It is also possible that treatment of hypertension and dyslipidemia could have influenced the results. The latter is unlikely because only ~1% of the patients received lipid-lowering treatment. Antihypertensive therapy varied from 15.5% in the NGT patients to 21.9% in the IFG/IGT group and 46.3% in the type 2 diabetic patients, with an even distribution of different treatment modalities (diuretics 28%, β-blockers 42%, calcium antagonists 21%, ACE inhibitors 29%). Finally, the number of deaths was relatively small, providing insufficient power to define the risk of total and cardiovascular death in the subgroups; therefore, the data regarding mortality should only be considered suggestive.

In conclusion, the clustering of cardiovascular risk factors called the metabolic syndrome (or, probably better, the dysmetabolic syndrome), based on the WHO definition, is seen in ~10% of subjects with NGT, ~50% of subjects with IFG/IGT, and ~80% of subjects with type 2 diabetes. It confers an increased risk of cardiovascular morbidity and mortality, and its identification may thus be important in the risk assessment and treatment of the patients.

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