Components of the Metabolic Syndrome and Risk of Cardiovascular Disease and Diabetes in Beaver Dam

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OBJECTIVE — To determine whether components of the metabolic syndrome precede the 5-year incidence of cardiovascular disease and diabetes.

RESEARCH DESIGN AND METHODS — A population of individuals aged 43–84 years was evaluated from 1988 to 1990 and again 5 years later. Medical history, blood pressure, and laboratory measures were obtained at both examinations following the same protocols. Subjects without diabetes were classified according to level of glycemia, high blood pressure, high-risk lipid levels, high uric acid levels, and proteinuria at baseline. History of incident myocardial infarction, angina, stroke, and diabetes was obtained at follow-up.

RESULTS — Of the 4,423 subjects without diabetes, 6.9% had elevated levels of glycemia, 18.4% had high blood pressure, 82.7% had high-risk lipid levels (either high serum total cholesterol or low HDL cholesterol or high ratio of these two levels), 27% had elevated uric acid levels, 33.2% had high BMI, and 3.3% had proteinuria (≥30 mg/dl). The risk of incident cardiovascular disease 5 years later increased with the number of the components present; 2.5% of those with one component developed cardiovascular disease, whereas 14.9% of those with four or more components developed cardiovascular disease. Of those with one component, diabetes developed in 1.1% 5 years later, whereas diabetes developed in 17.9% of those with four or more components.

CONCLUSIONS — Components of the metabolic syndrome are common and are associated with incident cardiovascular disease and diabetes after 5 years. Interventions to alter BMI, lipid levels, and blood pressure may decrease incident diabetes and cardiovascular disease.

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Many personal and environmental characteristics have been found to be associated with increased risk of cardiovascular disease (CVD) (1–3). Although some of these characteristics may occur alone (4), clustering of risk factors is not uncommon (5). The metabolic syndrome, defined by a cluster of risk factors including hypertension, central obesity, and dyslipidemia with or without hyperglycemia, seems to be associated with increased risk of macrovascular disease (5), which may exceed the sum of the risks incurred by each alone, although this view is not held universally (6–8). The features of the syndrome have been reported to precede the detection of overt diabetes (9) by as much as 10 years, at which time the known increased risk of CVD has been documented. Although other characteristics and exposures including smoking (10), alcohol intake (11), and physical activity (12) may further modify risk, it is our purpose to determine whether by focusing on the components of this syndrome or closely related characteristics we will find an increased risk of CVD and of overt diabetes and whether an increase in risk might be detected as soon as 5 years after assessing risk factor status. We evaluated this in a study initially identified to determine prevalence, incidence, and risk factors for age-related eye disease.

RESEARCH DESIGN AND METHODS

— A private census of the population of Beaver Dam, Wisconsin was performed from 1987 to 1988 (13). Individuals aged 43–86 years (n = 4,926) were evaluated during a 2.5-year period beginning March 1, 1988. Tenets of the Declaration of Helsinki were followed, institutional human experimentation committee approval was granted, and each subject provided informed consent. During the study visits, standard measurements and questionnaires were administered. All subjects identified at the initial census were invited for the second examination. Only those participating in the first and second examinations (n = 3,684; 2,092 women and 1,592 men) supplied information pertinent to the current article.

The follow-up examinations occurred 4.8 (±0.4) years after the first evaluations and were performed in such a way that participants were seen in approximately the same order as in the previous examinations.

Procedures at the follow-up were the same as at the baseline examinations. Details have been previously published (14–17). Blood pressure, height, and weight were measured. Participants were asked whether a doctor had ever told them that they had angina, heart attack, stroke, diabetes, and/or hypertension. This self-reported history of angina, heart attack, or stroke was used to define CVD at both visits. This was not confirmed by medical records. At the baseline examination, all subjects were asked to permit venipunc-

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Abbreviations: CVD, cardiovascular disease; WHO, World Health Organization.

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

Table 1—*Components of the metabolic syndrome at baseline*

Component	Definition	*n*	Mean ± SD	% Elevation
Elevated glycemia				6.9
Glucose	≥140 mg/dl	4,453	99.3 ± 16.3	2.5
Glycosylated Hemoglobin	≥7%	4,453	5.8 ± 0.7	5.4
High blood pressure				18.4
Systolic	≥160 mmHg	4,451	131.5 ± 20.3	9.1
Diastolic	≥90 mmHg	4,451	77.5 ± 11.0	13.1
High-risk lipid levels				82.7
Serum total cholesterol	≥200 mg/dl	4,452	233.5 ± 44.0	77.9
Serum HDL cholesterol	<35 (men), <39 (women) mg/dl	4,448	52.7 ± 17.7	15.9
Lipid ratio (Total/HDL)	>5.7 (men), >5.1 (women)	4,447	4.9 ± 1.9	33.4
Elevated BMI	>30 kg/m^2	4,423	28.5 ± 5.3	33.2
Elevated uric acid level	>7.0 mg/dl	4,453	6.0 ± 1.9	27.0
Proteinuria	≥30 mg/dl	4,437	—	3.3

ture to obtain serum for total cholesterol (18), HDL cholesterol (19), glycosylated hemoglobin (20), glucose (21), and uric acid (22). These tests, except for serum uric acid, were repeated at the 5-year follow-up. Subjects were not requested to fast. Proteinuria was defined as 30 mg/dl or more, as tested by a dipstick on a casual urine specimen that was collected at the time of the study examination.

Diabetes was defined as a previous history of diabetes (treated with insulin and/or oral hypoglycemic agents and/or diet) or hyperglycemia. Hyperglycemia here is defined as glycosylated hemoglobin >2 SDs above the mean for the appropriate age-sex group at the given examination or a casual blood glucose level >200 mg/dl (1.1 mmol/l). Newly diagnosed diabetes was defined as no previous history of diabetes in the presence of glycosylated hemoglobin that was >2 SDs above the mean for the appropriate age-sex group. There were 50 such persons. A total of 446 persons had diabetes at the time of the baseline examination. We excluded data from these individuals. Our definitions of the components of the metabolic syndrome were adapted from Alberti and Zimmet (7). The criteria they describe are impaired glucose intolerance, including frank diabetes or insulin resistance, and two or more of a list including elevated arterial pressure, elevated plasma triglyceride and/or low HDL cholesterol levels, central obesity or high BMI, and microalbuminuria. They indicate that other components have been described (e.g., hyperuricemia), but they do not include these in their definition. The components we included were level of glycemia, hypertension, serum total cholesterol level, serum HDL cholesterol level, ratio of serum total cholesterol to HDL cholesterol, serum uric acid level, obesity, and proteinuria (Table 1).

SAS statistical software was used to calculate χ^2 statistics, logistic regression, and Pearson correlations. Tests of trend were calculated by the Mantel-Haenszel method (23).

RESULTS — The baseline distribution of components of the metabolic syndrome that we have used to define elevated risk are shown in Table 1. Elevated serum total cholesterol and elevation of the ratio of total to HDL cholesterol (lipid ratio) derived from it are the most common risk factors, followed by elevated BMI, uric acid level, and blood pressure. For two of the lipid variables (serum HDL cholesterol and ratio of total to HDL cholesterol), different cutpoints are used to define "elevated" values for women and men. Elevated glycosylated hemoglobin level, albuminuria, and elevated blood glucose level were less common. For the remainder of this study, we discuss only elevated glycemia (either elevated serum glucose or elevated glycosylated hemoglobin), high-risk lipid levels (elevated total cholesterol, low HDL cholesterol, or elevated lipid ratio), and high blood pressure risk factor (high systolic or high diastolic blood pressure). The pairwise relationships of components of the metabolic syndrome within subjects are shown in Table 2. Many are significantly associated with the others. Correlation coefficients for continuously measured variables, in general, reflected the findings from the dichotomous analyses (correlations not shown in Table 2). Strongest correlations were between the lipid ratio and BMI (0.25), lipid ratio and uric acid level (0.34), BMI and uric acid level (0.31), and uric acid and HDL cholesterol levels (−0.30).

The population was examined 5 years after the baseline examination, at which time information about incident myocardial infarction, stroke, and angina during that interval was obtained. The incidences were 3.0% for myocardial infarction, 1.5% for stroke, and 4.0% for angina. These diagnoses are considered collectively as CVD. Incidences of CVD for each component are shown in Table 3. Because odds ratios were influenced by age and sex, the odds ratios are adjusted for these components. The greatest risks are associated with elevations in level of glycemia and presence of proteinuria.

We computed the relative risk of developing CVD by the number of these components at baseline (Table 4). The risk of incident CVD is approximately six times greater when four or more components are present, compared with when none of the components are present. Contributions of the individual components to clusters of factors associated with increased risk of CVD are shown in Table 5. For combinations of risk factors (1, 2, etc.), elevated glycemia occurred in 1.0% of those with one component, 6.1% of those with two components, 14.2% of those with three components, and 40% of those with four or more components. High-risk lipid levels occurred most commonly in the combinations of compo-

Table 2—*Pairwise relationships of components of the metabolic syndrome at baseline*

		Elevated glycemia		High blood pressure		High-risk lipid levels		Elevated BMI		Elevated uric acid level		Presence of proteinuria	
Component		%	*P* value	%	*P* value	%	*P* value	%	*P* value	%	*P* value	%	*P* value
Glycemia	Normal			18.0		82.3		32.2		25.8		3.2	
	Elevated			23.8	0.01	88.0	0.01	46.2	<0.001	43.5	<0.001	3.9	0.51
Blood pressure	Normal	6.4				82.1		30.3		25.6		2.6	
	Elevated	8.9	0.01			85.2	0.03	45.6	<0.001	33.3	0.001	6.5	<0.001
High-risk lipid	Absent	4.8		15.7				23.7		17.6		4.6	
levels	Present	7.4	0.01	19.0	0.03			35.2	<0.001	29	<0.001	3.0	0.03
BMI	Normal	5.6		15.0		80.2				20.2		3.0	
	Elevated	9.6	<0.001	25.4	<0.001	87.6	<0.001			40.5	<0.001	3.6	0.29
Uric acid level	Normal	5.4		16.8		80.5		27.0				2.5	
	Elevated	11.2	<0.001	22.7	<0.001	88.7	<0.001	49.9	<0.001			5.4	<0.001
Proteinuria	No	6.8		17.8		82.9		33.1		26.4			
	Yes	8.2	0.51	36.3	<0.001	76.0	0.03	37.3	0.29	44.5	<0.001		

nents that were associated with increased risk of CVD.

The relative risk of incident diabetes by each component is shown in Table 6. The measures of glycemia were most strongly related to incident diabetes; elevated BMI, high blood pressure, and elevated uric acid level also had significant relationships. Individuals with increasing numbers of risk factors are at increased risk of incidence of diabetes, such that those with four or more components are ~35 times as likely to develop the disease as those with none of the components at baseline (Table 7).

CONCLUSIONS — We have found that components of the metabolic syndrome, as we define them, in a population of individuals without diagnosed diabetes are relatively common and that they predict incident CVD and diabetes. The metabolic syndrome, originally described by Reaven (5), has been found in many ethnic groups (24). Insulin resistance may be the underlying pathophysiological basis of the syndrome. However, irrespective of understanding the specific metabolic relationships, the clinical importance of determining whether one, two, or more of these frequently measured components or variables closely related to them are most responsible for the link to subsequent macrovascular disease lies in whether they can be altered to reduce risk. Intervening directly on glycemia in people who at the moment do not carry a diagnosis of diabetes is probably not feasible. A more pragmatic approach might be to apply interventions aimed at altering levels of some of the other components of the metabolic syndrome (BMI, blood pressure, and lipid levels) in an effort to forestall incident heart disease and diabetes. Treating obesity, blood pressure, and higher lipid levels is no easy matter either, but there likely would be benefits to many disease end points not examined here and to the quality of life if interventions on these factors were successful. The recent Diabetes Prevention Trial (25) attests to the efficacy of an intervention to prevent diabetes based on altering these risk factors. Our data suggest the possibility that decreasing even one or two of the components of the metabolic syndrome may reduce the overall risk of incident CVD and diabetes. The components of the syn-

Table 3—*Incidence of CVD by components of the metabolic syndrome*

Component		*n*	Incidence (%)	Age- and sex-adjusted odds ratio (95% CI)	*P* value
Elevated glycemia	Normal	2,821	5.5		
	Elevated	150	14.0	2.31 (1.40, 3.82)	0.001
High blood pressure	Normal	2,464	5.8		
	Elevated	506	6.7	1.14 (0.77, 1.69)	0.50
High-risk lipid levels	Normal	535	3.4		
	Elevated	2,436	6.5	2.01 (1.21, 3.33)	0.01
Elevated BMI	Normal	1,983	5.6		
	Elevated	980	6.7	1.21 (0.88, 1.67)	0.24
Elevated uric acid level	Normal	2,257	4.8		
	Elevated	714	9.5	1.66 (1.19, 2.33)	0.003
Proteinuria	No	2,895	5.8		
	Yes	70	12.9	2.44 (1.16, 5.12)	0.02

Table 4—*Incidence of CVD by number of components of the metabolic syndrome*

No. of Components	*n*	Incidence (%)	Odds ratio (95% CI)	*P* value
0	318	2.5	1.0	
1	1,182	5.0	1.95 (0.91, 4.16)	0.08
2	885	6.1	2.05 (0.96, 4.40)	0.06
3	424	7.8	2.70 (1.22, 5.98)	0.01
4+	148	14.9	5.86 (2.51, 13.66)	<0.001

Table 5—*Contribution of each component of the metabolic syndrome to number of components in subjects at baseline examination (n = 4,406)*

No. of Components	*n*	Elevated glycemia (%)	Elevated blood pressure (%)	High-risk lipid levels (%)	Elevated uric acid level (%)	Elevated BMI (%)	Proteinuria (%)
0	418	0.0	0.0	0.0	0.0	0.0	0.0
1	1,689	1.0	2.9	87.2	3.3	5.2	0.5
2	1,335	6.1	22.3	92.4	31.8	43.9	3.5
3	704	14.2	38.5	96.9	67.3	77.7	5.4
4	260	40.0	74.6	98.5	90.4	92.3	18.5

drome are not only common, but the correlations among them are, in many cases, significant. It may be that intervention on one of a pair of components may have an effect on the other. Therefore, decreasing BMI may have a beneficial effect on blood pressure, lipid levels, and uric acid level. It is possible that intervening on blood pressure may also have beneficial effects on the kidney, at least with respect to proteinuria. Although we can, at best, only infer the possibility of such benefits, they are plausible.

We adapted, rather than adopted, the World Health Organization (WHO) criteria described by Alberti and Zimmet (7) for two reasons. The first is that our data were limited due to the study being initially designed primarily as a study of age-related eye disease. The second is that we were interested in the risks posed by the factors we examined in individuals from a general population who did not have overt diabetes. Although our study design is not ideal for evaluating the impact of a strictly defined study of the predictive ability of the WHO (or National Cholesterol Education Program) (26) criteria, we believe that our findings complement such studies.

We note several limitations to our investigation. Participants at the second examination were younger, had slightly lower serum cholesterol levels, had lower total HDL cholesterol ratios, had lower serum uric acid levels, were less likely to have CVD, and were less likely to have hypertension than those who participated only in the baseline exam. Our diagnoses of CVD are by self-report. This may lead to over- or under-reporting. Mortality from CVD is not included, because at this time, we do not have these data. This likely results in an underestimate of cardiovascular events because of those who gave no history of the condition but died of it. At this time, we cannot estimate the effect of this on incidence of CVD, nor can we determine its effects on the risk factor analyses. Lastly, our population is middle-aged, predominantly white, and rural. Therefore, we cannot make inferences beyond a similar group. These limitations notwithstanding, we have found that components of the metabolic syndrome singly, and in combination, are common and precede incident CVD and diabetes. This is despite the fact that the levels of the components we defined as high risk were not very high. In addition, increased risk can be observed as soon as 5 years later. This heightens the importance of determining ways to intervene on some or all of the components and implementing such interventions promptly.

Table 6—*Incidence of diabetes by components of the metabolic syndrome at baseline in Individuals without diabetes*

Component		*n*	Incidence (%)	Age- and sex-adjusted odds ratio (95% CI)	*P* value
Elevated glycemia	Normal	3,108	2.0		
	Elevated	182	29.1	18.33 (12.15, 27.67)	<0.001
High blood pressure	Normal	2,729	3.2		
	Elevated	560	5.2	1.65 (1.07, 2.55)	0.02
High-risk lipid levels	Normal	586	2.4		
	Elevated	2,704	3.7	1.55 (0.88, 2.74)	0.13
Elevated BMI	Normal	2,184	1.9		
	Elevated	1,094	6.7	3.75 (2.54, 5.55)	<0.001
Elevated uric acid level	Normal	2,447	2.7		
	Elevated	843	5.9	2.02 (1.36, 3.01)	<0.001
Proteinuria	No	3,201	3.5		
	Yes	82	3.7	0.98 (0.30, 3.19)	0.98

Table 7—*Incidence of diabetes by number of components of the metabolic syndrome*

No. of Components	*n*	Incidence (%)	Odds ratio (95% CI)	*P* value
0	338	0.6	1.0	—
1	1,291	1.1	1.75 (0.39, 7.72)	0.47
2	977	3.9	5.99 (1.44, 24.98)	0.01
3	492	5.9	9.37 (2.22, 39.59)	0.002
4+	173	17.9	33.67 (7.93, 142.96)	<0.001

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