The Metabolic Syndrome Is a Risk Indicator of Microvascular and Macrovascular Complications in Diabetes

Results from Metascreen, a multicenter diabetes clinic–based survey

THE METASCREEN WRITING COMMITTEE*

OBJECTIVE — We aimed at assessing the degree of association and the predictive power of the metabolic syndrome with regard to clinically detectable complications in patients with diabetes.

RESEARCH DESIGN AND METHODS — Metascreen is a cross-sectional survey of metabolic syndrome and clinically detected diabetes complications performed in 8,497 patients (7,859 with type 2 diabetes and 638 with type 1 diabetes) randomly chosen in 176 diabetes outpatient clinics throughout Italy. The metabolic syndrome was defined according to either the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) or the International Diabetes Federation (IDF) diagnostic criteria. Multivariate analyses of the association(s) between either AHA/NHLBI or IDF metabolic syndrome and clinical complications were performed. Receiver-operator characteristic (ROC) curves were constructed to compare the predictive power of the two sets of diagnostic criteria of the metabolic syndrome.

RESULTS — Either definition of the metabolic syndrome was an independent statistical indicator of the presence of nephropathy and neuropathy ($P < 0.02–0.01$) in type 1 diabetes and of all complications ($P < 0.0001$), including cardiovascular disease and retinopathy, in type 2 diabetes. For each complication, the ROC curves based on either AHA/NHLBI or IDF metabolic syndrome were similar to each other and to the ROC curves constructed with all continuous traits compounding the metabolic syndrome.

CONCLUSIONS — The metabolic syndrome, defined according to AHA/NHLBI or IDF diagnostic criteria, is an independent clinical indicator and may be involved in the pathogenesis of both macro- and microvascular complications of diabetes.

Diabetes Care **29:2701–2707, 2006**

Insulin resistance is a main feature of obesity and type 2 diabetes (1,2) and can be detected in hypertension and atherogenic dyslipidemia (high triglycerides and/or low HDL cholesterol) (3–6). Insulin resistance and/or compensatory hyperinsulinemia also are risk factor(s) for atherosclerosis and coronary heart disease (7–12). These and other observations have led to postulate the existence of the pathobiological entity metabolic syndrome, at the biologic core of which lies insulin resistance/hyperinsulinemia (13,14), which would play a significant role in promoting/accelerating atherosclerosis (15,16). The link between the metabolic syndrome, diabetes, and atherosclerosis may be due to negative cross-talk between angiotensin II and insulin signaling (17) and/or to TACE-TIMP3–mediated effects on the latter (18).

Several sets of criteria have been proposed to diagnose the metabolic syndrome, none of which has gained unanimous acceptance (19–21). In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III proposed a set of criteria, which, in spite of their limitations, are easily applicable in the clinical arena (22).

The NCEP position quite recently was revised by the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) (23), with unambiguos definitions of the diagnostic criteria for the four biological entities compounding the metabolic syndrome: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and elevated glucose. Over the last 3 years, several prospective studies (rev. in 24) were reanalyzed to gauge the role of the metabolic syndrome as a predictor of cardiovascular morbidity/mortality in nondiabetic individuals. As a whole, these studies seem to point to a significant role of metabolic syndrome in preceding/predicting vascular disease (24).

Recently, another set of criteria for the clinical diagnosis of the metabolic syndrome has been proposed by the International Diabetes Federation (IDF) (25). The latter requires abdominal obesity to be present and lowers the diagnostic thresholds for abdominal obesity (26). It is unknown whether the newly included individuals actually share the same cardiovascular risk as the individuals found to be affected by the metabolic syndrome according to the NCEP Adult Treatment Panel III criteria.

Type 2 diabetes represents a paradigmatic condition in which the metabolic syndrome is highly prevalent (27,28) and often precedes the onset of hyperglycemia. Furthermore, insulin resistance and the metabolic syndrome predict atherosclerosis in type 2 diabetic patients (12,27). Data regarding the prevalence of the metabolic syndrome in type 1 diabetes are less abundant. In the FinnDiane Study, conducted in patients with type 1 diabetes, the metabolic syndrome was a

Address correspondence and reprint requests to Bonadonna Riccardo, MD, Division of Endocrinology and Metabolic Diseases, Ospedale Civile Maggiore, Piazzale Stefani 1, 137126 Verona, Italy. E-mail: riccardobonadonna@tiscali.it.

Received for publication 8 May 2006 and accepted 28 August 2006.

*A complete list of the members of the Metascreen Writing Committee can be found in the APPENDIX.

Abbreviations: AHA, American Heart Association; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; NHLBI, National Heart, Lung, and Blood Institute; ROC, receiver-operator characteristic.

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

DOI: 10.2337/dc06-0942

frequent finding that increased with diabetic nephropathy and worse glycemic control (29).

A recent reappraisal of the metabolic syndrome, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes (30), pinpoints that the metabolic syndrome is an entity of little or no use in the diabetic patient and that no receiver-operator characteristic (ROC) curves have been published comparing the predictive/indicative power of the metabolic syndrome with that of the continuous variables compounding it (30).

We have used both the AHA/NHLBI and the IDF criteria (23,25) to diagnose the metabolic syndrome in diabetic patients participating in a cross-sectional survey conducted in 176 Italian diabetes clinics in 2002. We aimed to assess the prevalence of the metabolic syndrome in both type 1 and type 2 diabetic patients and its association with clinically detectable diabetes complications. We further built the appropriate ROC curves to compare the predictive power for clinically evident diabetes complications of either definition of the metabolic syndrome and of the continuous traits used for its detection.

RESEARCH DESIGN AND METHODS

— Metascreen is an observational, cross-sectional survey on the prevalence of the features of the metabolic syndrome (22,23,25) in diabetic patients in Italy.

One hundred and seventy-six outpatient diabetes clinics participated in the study between the end of August and the end of October 2002. During a 1-week period, randomly chosen by the data processing center (Idea99, Padova, Italy), each participating medium-sized clinic (≤100 patients per week) was instructed to report details of all consecutive patients referring to the clinic, with a requested minimum number of 40 patients. Larger clinics (>100 patients per week) were instructed to report details of one of every two patients (selection sequence: yes, no, yes, no, etc.) if the expected number of attending patients was between 100 and 200 patients and one of every three patients (sequence: yes, no, no, yes, no, no, etc.) if their expected attendance was between 200 and 300 patients, and so on. Investigators were asked to revise their clinical diagnosis and to exclude patients with other types of diabetes or gestational diabetes (31).

The following data were collected for each patient: demographic details (date of birth, sex), weight, height, type (1 or 2) and duration (years) of diabetes, waist circumference, systolic/diastolic blood pressure, fasting glycemia, glycated hemoglobin (with reference ranges), total and HDL cholesterol, triglycerides, creatinine, proteinuria, current hypoglycemic therapy(ies) (oral and insulin), other medical therapies (antihypertensive, hypolipidemic), clinical history of major cardiovascular events (myocardial infarction, stroke, coronary artery bypass graft/percutaneous transluminal coronary angioplasty revascularization intervention), and diabetes complications (micro- or macroalbuminuria, renal failure, retinopathy, peripheral and/or autonomic neuropathy). Diabetes complications, except retinopathy, were assessed in each clinic by a trained specialist in diabetology or other equivalent medical specialization. Diabetic retinopathy was assessed in each clinic by a trained specialist in eye diseases after funduscopic examination. The American Diabetes Association diagnostic criteria for clinical complications were used (32).

Raw data collected on case record forms were sent to the data processing center for storage and retrieval. Data were then scrutinized and queries sent to each diabetes clinic to correct obvious material errors, to recover missing data, especially those needed for the diagnosis of metabolic syndrome, or to resolve medical inconsistencies. All patients were considered to fulfill the criterion of high blood glucose according to the definitions of the metabolic syndrome (23,25).

Patients were diagnosed to have the AHA/NHLBI metabolic syndrome (23) when at least two of the following four criteria were fulfilled: *1*) waist circumference ≥102 cm in male subjects and ≥88 cm in female subjects; *2*) triglycerides ≥1.7 mmol/l, or specific treatment of this lipid abnormality; *3*) HDL cholesterol <1.03 mmol/l in male subjects and <1.29 in female subjects, or specific treatment for this lipid abnormality; or *4*) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or specific treatment of previously diagnosed hypertension.

Patients were diagnosed to have the IDF metabolic syndrome (25) when their waist circumference was ≥94 cm in male subjects and ≥80 cm in female subjects and at least one of the following three criteria was also fulfilled: *1*) triglycerides ≥1.7 mmol/l, or specific treatment for this lipid abnormality; *2*) HDL cholesterol <1.03 mmol/l in male subjects and <1.29 in female subjects, or specific treatment for this lipid abnormality; or *3*) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or specific treatment of previously diagnosed hypertension.

The study protocol was reviewed and approved by the ethics committee of the University of Padova, Italy. The nature and purpose of the study were explained to the patients, and informed consent was obtained from all participants.

Statistical analysis

Data were entered into a V-Basic data bank program for a Windows-based personal computer and analyzed by means of SAS version 6.2 statistical software. Data are expressed as means ± SD or as percentage values whenever suitable. The Student's *t* test was used to compare mean values of quantitative variables between the two groups (i.e., type 1 and type 2 diabetic patients), while distribution of discrete/qualitative variables were compared by χ^2 test.

A multivariate logistic regression model was applied in order to evaluate the role of either AHA/NHLBI or IDF metabolic syndrome, age at disease onset, duration of disease, HbA_{1c}, and LDL cholesterol as possible risk factors of specific and nonspecific diabetes complications.

ROC curves were constructed to compare the prognostic power of either definition of the metabolic syndrome and of the continuous variables used to diagnose it with regard to complications. The C statistic, which ranges between 0.5 and 1 and is higher the better the ROC curve, was used for comparison between the ROC curves. *A P* value <0.05 was considered statistically significant.

Role of the funding source

The study was designed and coordinated by the Metascreen Study Management Committee. Nonvoting representatives of the sponsor attended meetings of the management committee. Members of the Metascreen Writing Committee were responsible for preparation of the manuscript after all study-related data had been reviewed. The sponsor of the study had no role in data collection or data analysis. The Metascreen Writing Committee had full access to all the data and had final responsibility for the decision to submit for publication.

Table 1—*Demographic, anthropometric, cardiovascular, humoral, and clinical parameters of the study patients*

	Type 1 diabetes			Type 2 diabetes			
	Male subjects	Female subjects	All	Male subjects	Female subjects	All	*P* value
n	317	321	638	3,911	3,948	7,859	
Age (years)	47 ± 17	50 ± 18	48 ± 17	64 ± 11	66 ± 11	65 ± 11	<0.0001
Duration of disease (years)	15 ± 11	17 ± 12	16 ± 11	10 ± 8.0	11 ± 8.0	10 ± 8.0	<0.0001
BMI (kg/m^2)	24.8 ± 3.6	25.0 ± 5.5	24.9 ± 4.6	28.4 ± 4.3	30.0 ± 5.6	29.2 ± 5.1	<0.0001
Waist (cm)	89 ± 13	84 ± 16	87 ± 15	99 ± 13	98 ± 15	98 ± 14	<0.0001
Fasting plasma glucose (mmol/l)	10 ± 4.3	9.6 ± 3.7	9.8 ± 4.0	8.8 ± 2.8	9.0 ± 2.8	8.9 ± 2.8	<0.0001
A1C (%)	7.9 ± 1.7	8.0 ± 1.5	8.0 ± 1.6	7.5 ± 1.9	7.7 ± 1.5	7.6 ± 1.7	<0.0001
Creatinine (μmol/l)	87 ± 53	88 ± 53	88 ± 53	88 ± 44	89 ± 52	88 ± 44	0.287
Systolic blood pressure (mmHg)	132 ± 18	130 ± 19	131 ± 19	141 ± 18	143 ± 18	142 ± 18	<0.0001
Diastolic blood pressure (mmHg)	79 ± 10	78 ± 9.9	79 ± 10	82 ± 9.7	82 ± 10	82 ± 9.8	<0.0001
LDL cholesterol (mmol/l)	2.9 ± 0.9	3.0 ± 1.0	2.9 ± 0.9	3.2 ± 0.9	3.3 ± 1.0	3.2 ± 0.9	<0.0001
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.4	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	<0.0001
Triglycerides (mmol/l)	1.5 ± 0.8	1.4 ± 1.0	1.4 ± 0.9	1.9 ± 1.0	1.8 ± 0.9	1.9 ± 1.0	<0.0001
AHA/NHLBI metabolic syndrome (%)	24.5	43.2	33.7	58.8	80.8	69.5	<0.0001
IDF metabolic syndrome (%)	34.1	47.6	40.8	69.5	85.6	77.6	<0.0001

Continuous variables are means ± SD. *P* values refer to the comparison between type 1 and type 2 diabetic patients. Prevalence of IDF-defined metabolic syndrome was significantly higher ($P < 0.01$) than prevalence of AHA/NHLBI-defined metabolic syndrome in both types of diabetes.

RESULTS — The demographic, anthropometric, cardiovascular, and humoral parameters of the diabetic patients included in the Metascreen Study are reported in Table 1. As expected, type 2 diabetic patients were older and had wider waist circumference, higher blood pressure and triglycerides, and lower HDL cholesterol and HbA_{1c} than type 1 diabetic patients (all $P < 0.001$). The same differences also were evident when the patients were divided according to sex (data not shown). Sex was also associated with higher prevalence of the metabolic syndrome ($P < 0.001$).

The prevalence of the AHA/NHLBI metabolic syndrome was ~70% in type 2 diabetic patients, largely exceeding that observed in type 1 diabetic patients (Table 1). The prevalence of the IDF metabolic syndrome was significantly higher than the AHA/NHLBI metabolic syndrome in both type 2 and type 1 diabetes (Table 1). When the diabetes clinics were divided according to their geographical location (northern, central, or southern Italy), there was a rising prevalence of the metabolic syndrome, irrespectively of the definition used, going from northern to southern Italy. In type 1 diabetes, AHA/NHLBI metabolic syndrome rose from 29.7% to 39.3% and 37.6% and IDF metabolic syndrome from 38.2% to 43.8% and 43.0% in diabetes clinics from northern, central, and southern Italy, respectively. In type 2 diabetes, AHA/NHLBI metabolic syndrome rose from 66.6% to 69.8% and 72.9% and IDF metabolic syndrome from 75.4% to 76.0% and 79.9% in diabetes clinics from northern, central, and southern Italy, respectively. These trends were not statistically significant for type 1 diabetes ($P < 0.42$) but highly significant for type 2 diabetes ($P < 0.0001$).

Duration of disease (data not shown) and A1C were positively related to the prevalence of both AHA/NHLBI and IDF metabolic syndrome in both types of diabetes (data not shown). Both AHA/NHLBI and IDF metabolic syndrome were risk indicators of all complications, including cardiovascular disease, retinopathy, nephropathy, and neuropathy, not only in type 2 but also in type 1 diabetes (Table 2).

Since longer diabetes duration and higher A1C are expected predictors of diabetes complications, and both were associated with increased prevalence of both AHA/NHLBI metabolic syndrome and IDF metabolic syndrome (data not shown), we performed a multivariate logistic analysis to assess whether the metabolic syndrome is an independent risk marker of the presence of complications. We also included LDL cholesterol in this analysis because of its well-known role as a cardiovascular risk factor. Even in a multivariate model, either definition of the metabolic syndrome was strongly and independently associated with each diabetes complication in type 2 diabetes (Table 3). In type 1 diabetes, AHA/NHLBI metabolic syndrome was an independent risk indicator only of nephropathy and neuropathy, whereas IDF metabolic syndrome was an independent indicator of all complications except retinopathy, which fell just short of statistical significance (Table 3).

We compared the ROC curves for the prediction of complications based on models including the metabolic syndrome (either AHA/NHLBI or IDF definition) as a discrete variable. The ROC curves and the C statistics, which measure the area under the ROC curve, were very similar with both definitions of the metabolic syndrome (Table 4). Furthermore, the ROC curves of both AHA/NHLBI and IDF metabolic syndrome were almost superimposable to the ROC curves constructed with all continuous variables that compound the metabolic syndrome (data not shown).

CONCLUSIONS — In this article, we have reported the observations related to the detection of the metabolic syndrome, as assessed by either the AHA/NHLBI (23) or the IDF criteria, in a recent large survey conducted in diabetic patients attending 176 Italian diabetes clinics. The extensive number of diabetes clinics involved in this study, their fairly uniform spread across the country, and the average multivariable profile of the Metascreen type 2 diabetic patients, which was remarkably similar to other studies based on Italian diabetes clinics (12), all point out that this

Table 2—*Prevalence of metabolic syndrome in patients with and without complications*

	Type 1 diabetes			Type 2 diabetes		
		Metabolic syndrome			Metabolic syndrome	
	n	Absent (%)	Present (%)	*n*	Absent (%)	Present (%)
AHA/NHLBI metabolic syndrome						
Complication						
None	322	76.4	23.6	4,211	34.7	65.3
Retinopathy	218	58.3	41.7	1,732	24.7	75.3
Neuropathy	123	51.2	48.8	1,115	24.5	75.5
Nephropathy	172	48.3	51.7	1,777	21.7	78.3
Cardiovascular	59	45.8	54.2	1,302	23.3	76.7
IDF metabolic syndrome						
Complication						
None	322	70.8	29.2	4,211	26.9	73.1
Retinopathy	218	49.5	50.5	1,732	17.2	82.8
Neuropathy	123	44.7	55.3	1,115	18.2	81.8
Nephropathy	172	40.1	59.9	1,777	14.9	85.1
Cardiovascular	59	35.6	64.4	1,302	14.6	85.4

Total diagnosed according AHA/NHLBI and IDF criteria: type 1 diabetic patients $n = 638$, type 2 diabetic patients $n = 7,859$.

sample should be well representative of these patients.

The prevalence of the IDF metabolic syndrome was somewhat higher than the AHA/NHLBI metabolic syndrome, a finding that attained statistical significance in type 2 diabetes and is likely to reflect the lower diagnostic threshold for abdominal obesity adopted by the IDF. With both definitions, the prevalence of the metabolic syndrome was higher in women than in men. Whether this is a true biological phenomenon or a suboptimal choice of the gender-specific diagnostic thresholds is still unknown.

Table 3—*Odds ratios of diabetes complications in multivariate logistic analysis*

	Independent variables of the multivariate models				
Dependent variables	Age at diagnosis	Disease duration	A1C	LDL cholesterol	Metabolic syndrome
Diagnosed according to AHA/NHLBI criteria					
Type 1 diabetes					
Retinopathy	1.00 (0.41)	1.08 (<0.0001)	1.15 (0.033)	1.00 (0.83)	1.36 (0.15)
Nephropathy	0.99 (0.095)	1.05 (<0.0001)	1.04 (0.556)	1.00 (0.368)	3.00 (<0.0001)
Neuropathy	1.01 (0.069)	1.08 (<0.0001)	1.21 (0.015)	1.00 (0.709)	1.75 (0.021)
Cardiovascular disease	1.06 (<0.0001)	1.09 (0.0001)	1.11 (0.35)	0.99 (0.46)	1.72 (0.09)
Type 2 diabetes					
Retinopathy	1.00 (0.112)	1.08 (<0.0001)	1.16 (<0.0001)	1.00 (0.185)	1.41 (<0.0001)
Nephropathy	1.01 (0.001)	1.05 (<0.0001)	1.13 (<0.0001)	1.00 (0.187)	1.72 (<0.0001)
Neuropathy	1.01 (0.103)	1.06 (<0.0001)	1.18 (<0.0001)	1.00 (0.970)	1.24 (<0.0001)
Cardiovascular disease	1.03 (<0.0001)	1.06 (<0.0001)	1.09 (<0.0001)	1.00 (0.046)	1.50 (<0.0001)
Diagnosed according to IDF criteria					
Type 1 diabetes					
Retinopathy	0.99 (0.296)	1.08 (<0.0001)	1.16 (0.029)	1.00 (0.790)	1.49 (0.057)
Nephropathy	0.99 (0.052)	1.05 (<0.0001)	1.06 (0.429)	1.00 (0.345)	3.07 (<0.0001)
Neuropathy	1.01 (0.096)	1.08 (<0.0001)	1.22 (0.012)	1.00 (0.677)	1.76 (0.020)
Cardiovascular disease	1.05 (<0.0001)	1.09 (<0.0001)	1.12 (0.331)	1.00 (0.457)	2.05 (0.030)
Type 2 diabetes					
Retinopathy	1.00 (0.092)	1.08 (<0.0001)	1.16 (<0.0001)	1.00 (0.187)	1.49 (<0.0001)
Nephropathy	1.01 (0.002)	1.05 (<0.0001)	1.13 (<0.0001)	1.00 (0.197)	1.82 (<0.0001)
Neuropathy	1.01 (0.109)	1.06 (<0.0001)	1.18 (<0.0001)	1.00 (0.896)	1.62 (0.0093)
Cardiovascular disease	1.03 (<0.0001)	1.06 (<0.0001)	1.09 (<0.0001)	1.00 (0.033)	1.87 (<0.0001)

Data are OR (*P* value). ORs calculated for a unitary increase of each independent variable, except for the metabolic syndrome, for which the ORs show the change in risk associated with its presence.

Table 4—*C-statistics of the ROC curves of the association with each diabetes complication of the metabolic syndrome diagnosed with the AHA/NHLBI or IDF criteria in patients with type 2 diabetes*

	AHA/NHLBI-diagnosed metabolic syndrome		IDF-diagnosed metabolic syndrome	
	Male subjects	Female subjects	Male subjects	Female subjects
Retinopathy	0.707	0.719	0.708	0.719
Nephropathy	0.670	0.623	0.669	0.619
Neuropathy	0.684	0.692	0.683	0.691
Cardiovascular	0.665	0.681	0.671	0.68

No statistical differences between AHA/NHLBI and IDF metabolic syndrome were detected.

We detected a north-to-south gradient in the prevalence of the metabolic syndrome, which was statistically significant in type 2 diabetes. Whether the opposite gradient in socioeconomic status (33,34) existing in Italy plays a role or whether it is due to a different patient referral bias or to subtle differences in the genetic and ethnic background is currently unknown.

The metabolic syndrome, irrespective of its definition or of the type of diabetes (23), was associated with worse glucose control, longer duration of disease, and the presence of complications (Table 2). The former relationship may be due to either greater difficulties in achieving glucose control in patients with metabolic syndrome and/or an aggravating role of poor glucose control on the variables compounding the metabolic syndrome. For instance, it is well known that glucose control is inversely related to triglyceride levels (35). This was also true in type 1 diabetic patients, a finding that was superimposable to the FinnDiane Study (29). The latter relationship may be explained by either deterioration of glycemic control observed with longer duration of disease or an independent role of diabetes in unveiling the metabolic syndrome, or both. Since both glucose control and duration of disease are recognized risk factors of diabetes complications, a multivariate analysis was performed to assess the role of the metabolic syndrome. Irrespective of the definition, the metabolic syndrome was an independent risk factor of all complications in type 2 diabetes and of some in type 1 diabetes (Table 3). While this relationship was expected for cardiovascular complications (28) and is plausible for microvascular complications (36,37), the link to clinically evident diabetic neuropathy, to the best of our knowledge, is unprecedented. Impairments in microvascular function and structure and increased oxidant stress (38–40), which commonly accompanies the metabolic syndrome, may, at least partially, account for it.

There was a generalized trend of slightly higher complication odds ratios for IDF than for AHA/NHLBI metabolic syndrome (Table 3). This was more evident in type 1 than in type 2 diabetes (Table 3). Further studies will be needed to clarify this issue. However, the ROC curves and the C statistics of the prediction of complications were superimposable in IDF and AHA/NHLBI metabolic syndrome (Table 4), suggesting that these subtle differences may not have true clinical relevance. Furthermore, the ROC curves of both definitions of metabolic syndrome were very similar to the ROC curves of the variables compounding the metabolic syndrome, suggesting that most of the biological information may be captured by the dichotomous classification proposed by the AHA/NHLBI and IDF.

These findings, at variance with the contention that the metabolic syndrome is of little or no clinical value in the diabetic patient (30,41), support its clinical relevance in human diabetes (30). Indeed, the metabolic syndrome may be a simple, quick tool to stratify diabetic patients according to the expected severity of complications, irrespective of diabetes type.

Several limitations of our study should be recognized. First, our experimental design was cross sectional; therefore, our findings can attribute to metabolic syndrome a role of indicator, but not of predictor, of complications. Our survey, therefore, is more relevant as a hypothesis-generating rather than a hypothesis-testing study. In recent studies, the metabolic syndrome defined according to partially modified World Health Organization (27) or NCEP (42) criteria predicted cardiovascular events in patients with type 2 diabetes, but it is unknown whether this is also true for specific diabetes complications.

Other possible limitations include the lack of standardization of the clinical protocols to detect complications, the lack of statistical power in the analyses conducted in type 1 diabetic patients owing to the relatively low number of patients, the survival bias of a cross-sectional study, and a referral bias in the patients attending Italian diabetes clinics. As to the last two limitations, they would be expected to weaken the association between the metabolic syndrome and complications.

In summary, both the AHA/NHLBI (23) and the IDF (25) metabolic syndrome are strong, independent indicators of clinical complications in both type 1 and type 2 diabetes, in agreement with the tenet of a causal role of the metabolic syndrome (27,28) in the clinical complications of the diabetic patient. In this regard, the metabolic syndrome may substitute for its individual traits (waist circumference, atherogenic dyslipidemia, or blood pressure) in the diabetic patient. It remains to be determined whether these relationships detected in a cross-sectional survey also hold true in prospective studies.

Acknowledgments— The Metascreen study was funded with an unrestricted grant by GlaxoSmithKline, Spa, Italy.

We are indebted to Mara Roncaglia and Francesco Tessari from Idea99, Padova, Italy, for their invaluable technical and methodological support during the conduction of the Metascreen Study.

APPENDIX

Members of the Metascreen Writing Committee

Riccarcdo C. Bonadonna, Department of Biomedical and Surgical Sciences, Section of Endocrinology and Metabolic Diseases, University of Verona School of Medicine, Verona, Italy; Domenico Cucinotta, Department of Metabolic Diseases, University of Messina Medical School, Messina,

Italy; Domenico Fedele, Department of Metabolic Diseases, University of Padova Medical School, Padova, Italy; and Gabriele Riccardi and Antonio Tiengo, Department of Metabolic Diseases, University Federico II Medical School, Napoli, Italy.

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