Is the Third Component of Metabolic Syndrome Really Predictive of Outcomes in Type 2 Diabetic Patients?

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The use of the category of metabolic syndrome in patients with type 2 diabetes has been questioned by many authors (1,2). In fact, in most studies performed in the general population, the diagnosis of metabolic syndrome is associated with increased risk of diabetes (3–5) and, to a lesser extent, of cardiovascular disease (6); however, data on the impact of metabolic syndrome on cardiovascular morbidity and mortality in type 2 diabetic patients are inconclusive (7–11). Some authors found that, in type 2 diabetes, the presence of one further component of metabolic syndrome beyond diabetes confers a risk profile similar to that of full metabolic syndrome (12). Furthermore, the Adult Treatment Panel (ATP)-III definition of metabolic syndrome considers five parameters (fasting hyperglycemia, high blood pressure, low HDL cholesterol, hypertriglyceridemia, and high waist circumference) equally relevant for diagnosis, although each one of them is associated to a different extent with insulin resistance (13) and cardiovascular disease (14).

RESEARCH DESIGN AND METHODS

— An observational cohort study was performed on four consecutive series of type 2 diabetic patients resident in the city of Florence, Italy, with elevated blood pressure (sample A), hypertriglyceridemia (sample B), low HDL cholesterol (sample C), and elevated waist circumference (sample D), as defined by ATP-III criteria for metabolic syndrome (15), who were visited at the Diabetes and Metabolic Diseases Clinic of the Geriatric Unit of the University of Florence between 1 January 2000 and 31 December 2002. The four samples (A, B, C, and D), which were consecutively enrolled one after another (each during a period of 6 months) are described in Table 1.

All patients underwent a physical examination; weight and height were measured without shoes and in light clothing, while waist circumference (16) and blood pressure (17) were measured according to current recommendations. Laboratory determinations were performed in the central laboratory of Careggi Hospital, Florence, Italy, on blood samples drawn in the morning after an overnight fast. Total cholesterol, HDL cholesterol, and triglycerides were determined by an automated enzymatic method (Beckman, Brea, CA). Diagnosis of metabolic syndrome was performed using ATP-III criteria (15).

Information on all-cause mortality over 3 years after the first visit was obtained by the City of Florence Registry Office, which contains complete and updated records of all individuals living within city boundaries. For those who had moved away, queries were sent to the registry office of the new city of residence.

Statistical analysis

Normally and nonnormally distributed parameters were expressed as means ± SD and median (quartile range), respectively. χ^2 test was used for comparisons of categorical variables. Relative risk with 95% CIs were calculated, and a Cox regression was performed for multivariate analysis. All statistical analysis was performed with SPSS 12.0.1.

RESULTS

— The mean duration of follow-up was 32.9 ± 8.1, 32.5 ± 8.8, 33.6 ± 7,1, and 33.0 ± 8.2 months, in sample A, B, C, and D, respectively. Nineteen (3.4%), 22 (3.7%), 22 (4.1%), and 18 (3.6%) patients of sample A, B, C, and D, respectively, were lost at follow-up; their characteristics were not significantly different from those of the rest of the samples (data not shown). Forty (7.6%), 67 (11.8%), 76 (14.6%), and 61 (11.2%) deaths were recorded among patients enrolled in sample A, B, C, and D, respectively.

Among patients of sample A, those with metabolic syndrome at baseline did not show a significantly higher mortality than those without metabolic syndrome (7.9 vs. 6.4%); similar results were obtained in sample B (12.0 vs. 10.7%), C (19.0 vs. 14.0%), and D (11.9 vs. 11.1%). Diagnosis of metabolic syndrome was not associated with increased mortality in any of the samples studied, even after adjustment for age and sex at Cox regression analysis (data not shown).

In diabetic patients with elevated blood pressure (sample A), after adjustment for age and sex, separate Cox regression analyses showed that low HDL cholesterol (adjusted odds ratio [OR] 2.6 [95% CI 1.2–5.5]), but not hypertriglyceridemia and high waist circumference, was associated with higher mortality. Among diabetic patients with hypertriglyceridemia (sample B), low HDL cholesterol (sample C), and elevated waist circumference (sample D), mortality was associated with high blood pressure (2.7 [1.4–5.1], 1.4 [1.1–2.4], and 2.3 [1.3–4.2], respectively). No other component of metabolic syndrome was significantly associated with mortality in these sam-

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Abbreviations: ATP, Adult Treatment Panel.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Baseline characteristics of the four samples*

	Hypertension	Hypertriglycemia	Low HDL cholesterol	High waist circumference
Women	551 (59)	589 (50.9)	540 (53.8)	564 (77.7)
Age (years)	65.6 ± 10.0	65.0 ± 10.9	65.2 ± 11.1	66.2 ± 10.3
BMI (kg/m^2)	28.1 ± 4.6	28.6 ± 4.6	28.9 ± 4.7	30.9 ± 4.2
Waist (cm)	96.3 ± 9.0	97.7 ± 8.8	98.1 ± 8.9	101.1 ± 8.0
Men	98.5 ± 8.0	98.6 ± 6.8	99.8 ± 8.2	109.7 ± 5.5
Women	94.7 ± 9.2	95.7 ± 8.9	96.2 ± 9.1	98.6 ± 6.8
Duration of diabetes (years)	14.3 ± 11.3	13.1 ± 10.4	12.9 ± 10.3	13.4 ± 10.4
HbA_{1c} (%)	8.1 ± 1.9	8.3 ± 2.0	8.3 ± 2.0	8.1 ± 1.9
Total cholesterol (mg/dl)	217.3 ± 44.5	228.2 ± 47.0	215.6 ± 45.9	223.6 ± 46.1
HDL cholesterol (mg/dl)	49.7 ± 14.6	42.4 ± 11.6	36.4 ± 6.3	47.7 ± 13.5
Men	44.8 ± 13.3	39.1 ± 10.9	32.5 ± 4.3	40.6 ± 11.4
Women	53.1 ± 14.5	45.6 ± 11.4	39.8 ± 6.1	49.8 ± 13.4
Triglycerides (mg/dl)	154 (108–215)	212 (174–285)	151 (108–214)	160 (117–230)
Systolic blood pressure (mmHg)	154.0 ± 19.1	150.8 ± 21.4	149.7 ± 20.9	152.1 ± 20.4
Diastolic blood pressure (mmHg)	85.5 ± 11.7	84.9 ± 12.3	83.3 ± 11.7	85.7 ± 11.9
Therapy (%)				
Antiaggregants	34.0	35.4	30.4	31.0
ACE inhibitors/angiotensin	37.2	29.2	30.9	27.2
Statins	21.0	28.6	25.5	24.3
Insulin secretagogue	33.6	79.1	74.2	44.9
Metformin	36.3	38.2	34.9	38.5
Insulin	43.0	41.3	40.9	43.4
Metabolic syndrome components (%)				
Hypertension	100	48.2	38.2	51.4
HDL cholesterol	41.4	61.8	100	53.2
Triglyceride	51.5	100	67.2	55.7
Waist (ATP-III)	52.6	53.3	56.8	100

Data are *n* (%), means ± SD, or median (quartile range). Values of waist circumference and HDL cholesterol are also reported separately for each sex, considering that diagnostic criteria for metabolic syndrome for these parameters are different in women and men.

ples. Similar results were obtained after adjustment for duration of diabetes and medication, i.e., insulin, insulin sensitizers, insulin secretagogues, ACE inihibitors/angiotensin receptor blockers, and statins (data not shown). Combinations of any two metabolic syndrome components were not significantly associated with higher mortality in any of the four samples (data not shown).

CONCLUSIONS — The diagnosis of metabolic syndrome in patients with diabetes plus one more risk factor does not add any prognostic value in type 2 diabetic patients, in accordance with previous studies (12).

Hypertension is known as a major determinant of micro- and macrovascular disease in type 2 diabetes; in fact, treatment of elevated blood pressure substantially improves long-term morbidity and mortality (18). In diabetic patients with hypertriglyceridemia, low HDL cholesterol, or elevated waist circumference, hypertension was significantly associated with increased mortality. These data suggest that high blood pressure is a relevant independent risk factor. Conversely, the other components of metabolic syndrome do not seem to confer additional risk when two other ATP-III criteria for the syndrome are fulfilled. The notable exception is represented by low HDL cholesterol, which is associated with increased mortality in type 2 diabetic hypertensive patients only. These results need to be confirmed by further studies exploring cardiovascular morbidity.

The current ATP-III criteria for diagnosis of metabolic syndrome attribute the same relevance and diagnostic value to all the five parameters of the syndrome (5). The present analysis confirms that a different risk profile is determined by different combinations of metabolic alterations. For this reason, a diagnosis of metabolic syndrome based only on the unweighed number of components present in each patient, without considering each specific combination, could be inadequate for the prediction of risk level. This could explain the relatively unsatisfactory performance of diagnosis of metabolic syndrome in the prediction of cardiovascular morbidity and mortality in long-term epidemiological studies in type 2 diabetic patients.

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