Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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ORIGINAL RESEARCH

Risk factors associated with metabolic syndrome in type 2 diabetes mellitus patients according to World Health Organization, Third Report National Cholesterol Education Program, and International Diabetes Federation definitions

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Background: The availability of several definitions of the metabolic syndrome has created potential confusion concerning its prognostic utility. At present, little data exist about the risk factors associated with metabolic syndrome in diabetic patients.

Aim: To identify risk factors associated with metabolic syndrome in patients with type 2 diabetes mellitus according to three diagnostic criteria: World Health Organization (WHO), Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults – Adult Treatment Panel III (NCEP-ATP III), and International Diabetes Federation (IDF).

Subjects and methods: A logistic regression model was used to identify demographic, clinical, and lifestyle variables related with metabolic syndrome (N = 1259).

Results: Hypertension, dyslipidemia, and glycosylated hemoglobin (HbA_{1c}) ≥7% were associated with increased risk of WHO-defined metabolic syndrome (odds ratio [OR], 2.33; 95% confidence interval [CI]: 1.60–3.40; OR, 1.79 95% CI: 1.25–2.55; and OR, 1.58; 95% CI: 1.12–2.22, respectively). The risk of presenting metabolic syndrome according to NCEP-ATP III criteria was increased in female patients (OR, 2.02; 95% CI: 1.37–2.97), elevated fasting glucose levels (OR, 5.99; 95% CI: 3.56–10.07), dyslipidemia (OR, 2.28; 95% CI: 1.57–3.32), hypertension (OR, 2.36; 95% CI: 1.59–3.53), and endocrine disorders (OR, 1.64; 95% CI: 1.06–2.57). For the IDF criteria, female patients and patients with left ventricular hypertrophy or insulin treatment were at higher risk of metabolic syndrome (OR, 4.00; 95% CI: 2.35–6.80; OR, 2.72 95% CI: 1.22–6.04; and OR, 1.96 95% CI: 1.24–3.11, respectively).

Conclusions: The risk factors for metabolic syndrome in type 2 diabetes mellitus patients are highly dependent on the criteria used to define the syndrome, supporting the need for a single clinically useful and epidemiologically useful definition.

Keywords: metabolic syndrome, type 2 diabetes mellitus, epidemiologic studies, risk factors

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Introduction

Patients with metabolic syndrome, also known as cardiometabolic syndrome or insulin resistance syndrome, are at greater risk of cardiovascular disease regardless of a previous history of cardiovascular events.[1,2] This is particularly relevant in patients with type 2 diabetes mellitus, who are at even greater cardiovascular risk.[3] In fact, cardiovascular complications are the most common cause of morbidity and mortality in this population.[4]

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The availability of several definitions of metabolic syndrome has created potential confusion concerning its prognostic utility. At present, little data exist about the risk factors associated with metabolic syndrome in diabetic patients.[5,6] The aim of this analysis was to identify the risk factors associated with metabolic syndrome in a large sample of patients with type 2 diabetes mellitus in Spain according to three diagnostic criteria: World Health Organization (WHO), the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults – Adult Treatment Panel III (NCEP-ATP III), and the International Diabetes Federation (IDF). The main difference between these diagnostic criteria lies in the way in which the various components for the diagnosis are grouped and combined. The WHO criteria focus on the presence of diabetes, glucose intolerance or insulin resistance together with the presence of at least two other components from a list of five components. On the other hand, the NCEP-ATP III criteria give the same weight to abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia and low HDL-cholesterol (three or more of these components must be present for a diagnosis). Finally, the IDF criteria are similar to NCEP-ATP III although emphasizing the presence of abdominal obesity – with cutoff points tailored to ethnic origin – compared with other four components of which at least two or more must be present.[7]

Subjects and methods

Study design, subjects, and methods have been described previously.[7] This is a secondary analysis of the data from a nationwide, cross-sectional, naturalistic, multicenter study carried out in outpatient clinics in Spain. The study was performed between November 2004 and July 2005. Included patients had type 2 diabetes mellitus diagnosed according to the American Diabetes Association (ADA) criteria and were aged 18 years or older. The local ethical review board of the Hospital Clínico San Carlos (Madrid, Spain) provided approval of the study protocol and the study was conducted in accordance with the principles of the Declaration of Helsinki.

We explored the associations between significant demographic, clinical, and lifestyle variables and the prevalence of metabolic syndrome (diagnosed according to WHO, NCEP-ATPIII, and IDF criteria) by means of a chi-square test for categorical variables and a Student's *t*-test for continuous variables. The sociodemographic and lifestyle variables included in the analysis were age, geographical region, education, smoking status, and physical activity; the clinical variables were body mass index (BMI), glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) values, diagnosis of dyslipidemia, hypertension, cardiovascular disease, heart failure, left ventricular hypertrophy, or existing comorbidities. All the variables with a P value < 0.1 in the bivariate analysis were included as independent variables in a multivariate logistic regression model. This cut-off point was chosen to ensure that all possibly related variables were included in the logistic regression model.

Results

Out of the 1345 patients selected, 1259 met the inclusion criteria and participated in the study (622 from primary care and 637 from internal medicine settings). Patients' mean age (standard deviation [SD]) was 64.7 (10.7) years, and 57.1% of patients were male. Physical activity was low in 61.9% of patients, of whom 31.4% had a sedentary lifestyle. Mean time (SD) from type 2 diabetes mellitus diagnosis was 7 years (7.3). The majority of patients were on diet and exercise (88.2%), and 75.9% of the sample was receiving oral antihyperglycemic medications (OAM). Twenty percent were on insulin treatment. In addition, a total of 70.8% of patients had been diagnosed with hypertension, dyslipidemia (67.1%), or left ventricular hypertrophy (12.3%).

Results from the logistic regression analyses are shown in Table 1. The presence of metabolic syndrome according to the WHO definition was significantly associated with age, intense and moderate physical activity, dyslipidemia, hypertension, treatment with OAM, and HbA_{1c} levels $\geq$7%. The existence of dyslipidemia, hypertension, and HbA_{1c} $\geq$7% in patients was related to higher odds ratios for metabolic syndrome. In contrast, older age ($\geq$65 years) and intense and moderate physical activity attenuated the risk of metabolic syndrome. For NCEP-ATP III definition, age, gender, moderate and intense physical activity, elevated FPG levels, dyslipidemia, hypertension, treatment with OAM, and the presence of endocrine disorders were independently associated with metabolic syndrome. The risk of metabolic syndrome was elevated in females (twofold), patients with elevated fasting plasma glucose levels (sixfold), dyslipidemia, hypertension, and endocrine disorders. Finally, the prevalence of metabolic syndrome as per IDF definition was associated with gender, moderate physical activity, insulin treatment, and left ventricular hypertrophy. Women (fourfold), patients not treated with insulin, and patients with left ventricular hypertrophy were at higher risk of IDF-defined metabolic syndrome than men, patients treated with insulin, and patients without left ventricular hypertrophy, respectively.

Table 1 Odds ratios for having metabolic syndrome according to WHO, NCEP-ATPIII, and IDF definitions

	WHO OR [95% CI]	NCEP-ATPIII OR [95% CI]	IDF OR [95% CI]
Age (≥65 years vs <65 years)	0.48 [0.34–0.69]	0.59 [0.41–0.87]	–
Gender (female vs male)	–	2.02 [1.37–2.97]	4.00 [2.35–6.80]
Physical activity			
Low (<2 h/week vs sedentarism)	0.82 [0.52–1.27]	0.66 [0.40–1.09]	0.62 [0.35–1.09]
Moderate (2–4 h/week vs sedentarism)	0.43 [0.27–0.67]	0.43 [0.26–0.72]	0.42 [0.24–0.74]
Intense (>6 h/week vs sedentarism)	0.44 [0.26–0.76]	0.30 [0.17–0.53]	0.53 [0.27–1.04]
HbA_{1c} (>7% vs ≤7%)	1.58 [1.12–2.22]	1.08 [0.74–1.56]	–
Fasting glucose (elevated vs normal)	1.36 [0.78–2.35]	5.99 [3.56–10.07]	–
Dyslipidemia (yes vs no)	1.79 [1.25–2.55]	2.28 [1.57–3.32]	–
Hypertension (yes vs no)	2.33 [1.60–3.40]	2.36 [1.59–3.53]	–
Treatment with OAM (yes vs no)	1.54 [1.04–2.29]	1.63 [1.07–2.48]	–
Treatment with insulin (yes vs no)	–	–	1.96 [1.24–3.11]
Endocrine disorders (yes vs no)	1.44 [0.97–2.12]	1.64 [1.06–2.57]	–
Left ventricular hypertrophy (yes vs no)	1.68 [0.95–2.97]	1.32 [0.73–2.41]	2.72 [1.22–6.04]

Note: Variables not included in the model due to lack of statistical significance in the bivariate analysis.
Abbreviations: WHO, World Health Organization; NCEP-ATPIII, Third Report National Cholesterol Education Program; IDF, International Diabetes Federation; OR, odds ratio; OAM, oral antihyperglycemic medication; CI, confidence interval; HbA_{1c}, Hemoglobin A_{1c}.

The risk of having metabolic syndrome for women with type 2 diabetes mellitus was higher by the IDF criteria than the NCEP-ATP III criteria. An older age (≥65 years) and intense physical activity appeared to be protective factors against metabolic syndrome according to both WHO and NCEP-ATP III, whereas the presence of dyslipidemia, hypertension, and treatment with OAM showed similar increased risk by both diagnostic definitions. Finally, moderate physical activity seemed to be associated with reduced risk by NCEP-ATP III, IDF, and WHO definitions of metabolic syndrome.

Discussion

Previously published data from this study showed that in this population, the prevalence rates of metabolic syndrome according to WHO, NCEP-ATP III, and IDF were different (71.5%, 78.2%, and 89.5%, respectively).[7] Further, the data presented here provide evidence that in subjects with type 2 diabetes mellitus, the existence of dyslipidemia, hypertension, and HbA_{1c} levels of ≥7% increases the risk of presenting metabolic syndrome, according to WHO-defined criteria. For the NCEP-ATP III-defined metabolic syndrome, the risk is increased in women, subjects with elevated FPG levels, dyslipidemia, hypertension, and endocrine disorders. For the IDF criteria, women, patients treated with insulin, and patients with left ventricular hypertrophy (may be related to hypertension) are at higher risk of metabolic syndrome. Although there is some disparity in the degree of physical activity related to the NCEP-ATP III, IDF, and WHO definitions, it seems that exercise training would be associated in this study with a decreased risk of metabolic syndrome. This is the first study to show that metabolic syndrome, according to all three definitions (WHO, NCEP-ATP III, and IDF), in a large sample of Spanish patients with type 2 diabetes, is independently associated with different risk factors (metabolic and non-metabolic) depending on the diagnostic criteria used, likely due in part to the differences in the cut-off points. Nevertheless, all three criteria provided greater odds ratios for the cardiovascular risk factors studied. In fact, previous studies have reported an increased cardiovascular risk associated with the presence of metabolic syndrome.[8,9] This is not surprising since metabolic syndrome contains well-established cardiovascular risk factors such as hypertension and dyslipidemia.

In summary, the risk factors associated with the presence of metabolic syndrome in a population with type 2 diabetes mellitus are highly dependent on the criteria used to define metabolic syndrome, supporting the need for a single common clinically and epidemiologically useful definition of metabolic syndrome. The identification and clinical management of the high-risk groups will contribute significantly to metabolic syndrome prevention in patients with type 2 diabetes mellitus.

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