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Metabolic syndrome does not increase angiographic restenosis rates after drug-eluting stent implantation

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Abstract

Metabolic syndrome (MS) is associated with an increased risk of coronary heart disease, stroke, and cardiovascular mortality; but its effect on patients undergoing cardiac revascularization is still unclear. Robust evidence demonstrates that diabetes mellitus and insulin resistance are among the main risk factors for restenosis in patients requiring percutaneous myocardial revascularization. The recent advent of drug-eluting stents (DESs) has significantly reduced the incidence of restenosis compared with bare-metal stents, both in nondiabetic and in diabetic patients. The aim of the study was to evaluate the effect of MS on the risk of binary restenosis in DES implant recipients. One hundred eighty-nine recipients of successful DES implants performed between January and March 2005 for stable coronary artery disease underwent 1-year clinical and angiographic follow-up. Body mass index (BMI), blood pressure, fasting blood glucose, and lipid profile were determined. *Metabolic syndrome* was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria, with the waist criterion being substituted by a BMI $\geq$28.8 kg/m^2. Metabolic and anthropometric information for MS diagnosis was available for 148 of 189 patients; 87 of 148 patients (58%) had MS. Patients with MS had higher BMI (28.4 ± 3.8 vs 26 ± 2.7 kg/m^2, $P < .0001$), systolic blood pressure (133 ± 14 vs 124 ± 14 mm Hg, $P = .0004$), and fasting glucose (113 ± 37 vs 92 ± 17 mg/dL, $P < .0001$). They also had higher serum triglycerides (154 ± 94 vs 113 ± 43, $P = .0018$) and lower high-density lipoprotein cholesterol levels (39 ± 9 vs 46 ± 10, $P < .0001$). Rates of restenosis (10.5% vs 8.1%, P = not significant [NS]), target vessel revascularization (10.5% vs 11.3%, P = NS), and major adverse cardiac events (11.6% vs 14.5%, P = NS) were not significantly different in patients with MS compared with those without MS, nor was any association found between increased end point risk and presence of MS. When patients were subdivided into 6 subgroups by the presence of 0, 1, 2, 3, 4, or 5 of the MS components, restenosis rates were not significantly different among subgroups. In conclusion, MS is not associated with higher rates of restenosis, target vessel revascularization, or major adverse cardiac events; and no additional MS feature was associated with an increased risk.

1. Introduction

Metabolic syndrome (MS) is characterized by concurrent abdominal obesity, dyslipidemia, hypertension, impaired glucose tolerance, and/or diabetes [1-3]. Its prevalence, which is related to age, gender, and ethnic group, is rising in the United States and worldwide [4-6]. The unadjusted and age-adjusted prevalence in the United States is 21.8% and 23.7%, respectively [7], whereas its age-standardized prevalence in European cohort studies is lower, being slightly higher in men than in women (15.7% vs 14.2%) [5]. In an Italian cohort of adult subjects [8], the prevalence of MS was 18% in women and 15% in men.

The syndrome involves a well-explored cluster of risk factors for cardiovascular disease (CVD) including insulin resistance and a proinflammatory and prothrombotic state; it is associated with an increased risk of coronary heart disease, stroke, and cardiovascular mortality [9-11]. Patients with MS have a 2-fold higher risk of CVD even if they do not have diabetes [12]. In contrast, the effect of MS on patients undergoing cardiac revascularization, particularly percutaneous coronary interventions, is still unclear.

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Metabolic syndrome is not associated with target vessel revascularization (TVR) or clinical restenosis after percutaneous coronary intervention with bare-metal stents (BMSs) [13], whereas there is robust evidence that diabetes mellitus and insulin resistance are 2 of the main risk factors for restenosis in patients requiring myocardial revascularization [14-16].

The introduction of drug-eluting stents (DESs) has significantly reduced restenosis rates compared with BMSs both in nondiabetic and in diabetic patients [17-20] by reducing neointimal hyperplasia due to smooth-muscle cell proliferation and migration and extracellular matrix production.

The aim of our study was to evaluate the effect of MS on the risk of binary restenosis in DES implant recipients.

2. Methods

In 2004, a prospective DES Registry was set up at Lancisi Hospital, Ancona, to evaluate the safety and efficacy of DESs using a protocol with a 12-month angiographic follow-up. The Registry was approved by the local ethics committee, and the informed consent of each patient was obtained. In this study, we analyze the data from 189 consecutive recipients of successful DES implants performed for stable coronary artery disease who underwent 1-year clinical and angiographic follow-up between January and March 2005 to assess the role of MS in restenosis.

Patients were treated for one or more lesions, receiving at least one sirolimus-eluting (Cypher; Cordis, Johnson & Johnson, Miami Lakes, FL) or paclitaxel-eluting stent (Taxus Express; Boston Scientific, Natick, MA) of various diameters and lengths depending on the angiographic features of the target vessel. The diagnostic work-up comprised evaluation of diabetes, hypertension, and dyslipidemia. Physical examination included body weight, height, and blood pressure. Body mass index (BMI) was calculated using the formula weight (in kilograms)/height (in meters squared). Because waist circumference data were not available for all patients, a cutoff BMI $\geq$28.8 kg/m^2, which is equivalent to a waist circumference of 102 cm in men [13,21,22], was adopted to define abdominal obesity.

Blood samples were collected after overnight fasting before DES placement to determine serum total and high-density lipoprotein cholesterol (HDL-C), triglycerides, and glucose. Laboratory tests were performed using standard enzymatic methods.

Patients with MS were identified by any combination of 3 or more of the following components: (1) *obesity* (defined as a BMI $\geq$28.8 kg/m^2); (2) triglyceride levels $\geq$150 mg/dL or current use of lipid-lowering medication; (3) HDL-C <40 mg/dL in men and <50 mg/dL in women; (4) systolic blood pressure $\geq$130 mm Hg and/or diastolic blood pressure $\geq$85 mm Hg, or current use of antihypertensive medication; and (5) fasting glucose level $\geq$110 mg/dL or previously diagnosed type 2 diabetes mellitus.

Follow-up 1 year from stent placement was by clinical and angiographic evaluation of the rates of binary angiographic restenosis, TVR, and major adverse cardiac events (MACE), which included TVR, acute coronary syndrome (ACS), and cardiovascular death.

Binary restenosis was defined as stenosis involving $\geq$50% of the lumen diameter and was classified as in-stent when found inside the stent and as edge restenosis when located within the stent's distal or proximal 5-mm segment.

2.1. Statistical analysis

Data are expressed as mean ± SD. Categorical variables were compared with the Fisher exact test. Continuous variables were compared using the Student unpaired *t* test. The relative risk for restenosis was calculated. Significance was set at $P < .05$. Statistical analyses were performed using the Statview 4.1 package (Abacus Concepts, Berkeley, CA).

3. Results

Metabolic and anthropometric information for MS diagnosis was available for 148 of the 189 patients. Statistical analysis was performed on the data from 148 patients. There were 118 men and 30 women, with a mean age of 61 ± 11 years. Eighty-six patients (58%) had MS according to the above-described criteria, hypertriglyceridemia (n = 119, 80%) and hypertension (n = 109, 74%) being the most prevalent and obesity (n = 41, 27%) the least prevalent of the 5 MS components. Seventy-seven patients (52%) had low HDL-C; 65 (44%) had impaired fasting glucose or diabetes. Diabetes was slightly less prevalent than in the principal DES trials and registers (n = 30, or 20% vs 23%-28% in references 17-20).

Patients' baseline metabolic data are reported in Table 1. Subjects with MS had greater BMI (28.4 ± 3.8 vs 26 ± 2.7 kg/m^2, $P < .0001$), higher systolic blood pressure (132 ± 14 vs 124 ± 14 mm Hg, $P = .0004$), and higher fasting glucose levels (113 ± 37 vs 92 ± 17 mg/dL, $P < .0001$). They also

Table 1
Baseline metabolic data

	Patients with MS (n = 86)	Patients without MS (n = 62)	P[a]
Age (y)	62.7 ± 10.5	59.9 ± 11.8	.14
BMI	28.4 ± 3.8	26 ± 2.7	<.0001
SBP (mm Hg)	132 ± 14	124 ± 14	.0004
DBP (mm Hg)	76 ± 10	73 ± 9	.07
Fasting glucose (mg/dL)	113 ± 37	92 ± 17	<.0001
Cholesterol (mg/dL)	172 ± 40	183 ± 41	.13
HDL-C (mg/dL)	39 ± 9	46 ± 10	<.0001
Triglycerides (mg/dL)	154 ± 94	113 ± 43	.0018

Data are expressed as means ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

[a] Unpaired Student *t* test.

Table 2
Angiographic and clinical follow-up

	Patients
MACE	19 (13%)
CV death	0
ACS	5 (3%)
Edge restenosis	1
Subacute thrombosis	1
De novo lesion in other vessel(s)	3
TVR	16 (11%)
De novo stenosis	3
Restenosis	12
Subacute thrombosis	1
Restenosis	14 (9%)
In-stent restenosis	6
Edge restenosis	6
Occlusion	2
Mild neointimal hyperplasia	7

Data are expressed as number (percentage). CV indicates cardiovascular.

had higher serum triglycerides (154 ± 94 vs 113 ± 43, $P = .0018$) and lower HDL-C levels (39 ± 9 vs 46 ± 10, $P < .0001$). Single lesion revascularization was performed in 62% of patients, whereas 38% underwent multiple vessel procedures.

At a mean follow-up of 12 months (Table 2), 19 patients had had MACE. There were no cases of cardiovascular death. Five (3%) patients had ACS, and 16 (11%) required TVR. Three cases of ACS were due to a new lesion in a different vessel; and 2, which are included in the cases of TVR, were due to edge restenosis and to subacute thrombosis 7 days from stent implantation, respectively. The TVRs were 12 cases of restenosis, 3 de novo lesions in the same vessel at a distance from the stent, and the subacute thrombosis mentioned above. Fourteen (9%) patients developed binary restenosis, 6 for in-stent lesions, 6 for edge lesions, and 2 asymptomatic patients due to occlusion that did not need revascularization for the presence of a copious collateral circulation. Seven patients exhibited mild hyperplasia, involving <50% of the lumen diameter. There were no cases of acute or late stent thrombosis.

Rates of restenosis (10.5% vs 8.1%), TVR (10.5% vs 11.3%), and MACE (11.6% vs 14.5%) were not significantly different in patients with MS compared with those without MS; and there was no association between increased end point risk and MS (Table 3).

Table 3
Risk of restenosis, TVR, and MACE according to the presence of MS

	MS	No MS	P[a]	RR	95% CI
Restenosis	9 (10.5%)	5 (8.1%)	NS	1.30	0.46-3.37
TVR	9 (10.5%)	7 (11.3%)	NS	0.93	0.36-2.35
MACE	10 (11.6%)	9 (14.5%)	NS	0.80	0.35-1.85

Data are expressed as number (percentage). RR indicates relative risk; CI, confidence interval; NS, not significant.

[a] Fisher exact test.

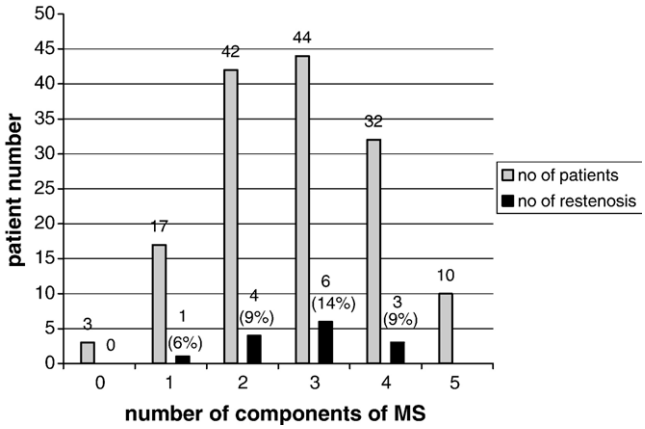

Fig. 1. Subdivision of the population into 6 groups based on rising number of associated MS components and prevalence of restenosis in each group.

When patients were subdivided into 6 subgroups based on the presence of 0, 1, 2, 3, 4, or 5 components, those with 2 and 3 components were the more numerous and the groups with none or 5 features were the less numerous. The rate of restenosis was not significantly different among subgroups (Fig. 1).

4. Discussion

We evaluated the effect of MS on 1-year rates of restenosis, TVR, and major cardiac events in DES implant recipients. Rates were not significantly different in subjects with MS compared with those without the syndrome, nor was the presence of a greater number of MS components associated with an increased CVD risk. These data are in line with previous studies of clinical restenosis in MS patients [11], but regard exclusively DES implants and also include the evaluation of angiographic restenosis.

A preliminary consideration with reference to the study design is that the very concept of MS has been criticized by some authors, who deny that MS can be defined with accuracy and consider the current diagnostic criteria ambiguous and incomplete [23]. Furthermore, despite the strong evidence for an association between MS and higher cardiovascular morbidity and mortality, the value of MS as a risk marker for CVD has recently come under attack. In particular, the debate centers on whether MS as a metabolic alteration cluster entails an additional risk compared with its single components; in addition, despite the fact that the diagnostic criteria for MS are well-known cardiovascular risk factors when taken singly, it is unclear whether their use as mere dichotomous variables (presence/absence) can provide an accurate assessment of cardiovascular risk. Investigations into whether the assessment of each factor as a continuous variable is a better predictor would be helpful.

With regard to in-stent restenosis, it has been demonstrated that the principal underlying mechanisms are neointimal tissue proliferation resulting from growth and migration of vascular smooth-muscle cells and the

inflammatory response of the vessel wall [24]. On the other hand, several investigations have shown that insulin resistance and the proinflammatory state characteristic of MS play an important role in enhancing neointimal tissue proliferation after coronary stent implantation [16,25]. In particular, intravascular ultrasound studies of nondiabetic patients have documented greater neointimal proliferation poststenting in subjects with impaired glucose tolerance and that the sum of insulinemia after oral glucose tolerance test was an important predictor of the risk of restenosis [25]. In another study [26], patients who experienced restenosis after coronary stenting had higher insulin, homeostasis model assessment index, and leptin; in these subjects, insulin sensitivity indices correlated independently with the minimal lumen diameter at multiple regression analysis. These data suggest that adoption of more sophisticated markers of MS, for example, insulinemia and insulin resistance indices, may enable a more accurate assessment of the risk of restenosis and of CVD in general.

In fact, our data do not indicate that MS involves an additional risk of restenosis, as already established for BMSs [13]; however, even with the adoption of the more stringent definition of MS suggested above, the antiproliferative and anti-inflammatory effects of DESs might result in offsetting any additional risk induced by MS.

Because DESs have reduced restenosis rates and delayed its peak to about a year after implantation, the small number of patients included in this study and the 12-month follow-up may have led to underestimating these events. The absence of a clear correlation between rising number of associated MS components and restenosis rate may be a consequence of the small patient sample, especially in the subgroups with none and all of the 5 MS components.

In the last year, DESs have come under attack because of a putatively higher risk of late stent thrombosis compared with BMS [27-29]. There was a single case of subacute thrombosis and no case of acute or late thrombosis among our patients. Late thrombosis is a rare event, whose main risk factor is discontinuation of antiplatelet therapy. This fact, coupled to the small sample size and a follow-up limited to the period of dual antiplatelet drug regimen, prevents any definitive conclusion about late stent thrombosis.

Another limitation of our study is that waist circumference values were not available for all patients, leading to the adoption of a BMI value of $\geq$28.8 kg/m^2 as a surrogate of central obesity. Although this value has already been used as an equivalent of abdominal obesity [13,21,22], it may result in misclassification of abdominal obesity. Anyway, it has recently been observed that DESs attenuate the increased risk associated with obesity compared with BMSs, in particular by offsetting the effect of body weight in the medium term [30].

In conclusion, these results indicate that MS per se does not involve an additional risk of restenosis in DES-implanted patients. They also have important implications given the high prevalence of MS and confirm the effectiveness of DESs also in MS patients in the presence of appropriate clinical indications. The indication for a DES implant is therefore subject to case-by-case assessment based on the severity of the individual metabolic alterations.

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