Genetic, clinical and experimental aspects of restenosis : a biomedical perspective

Monraats, P.S.

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Metabolic syndrome and risk of restenosis in patients undergoing percutaneous coronary intervention

Jamal S. Rana, Pascalle S. Monraats, Aeilko H. Zwinderman, Moniek P. M. de Maat, John.J.P. Kastelein, Pieter A.F. Doevendans, Robbert J. de Winter, René A. Tio, Rune R. Frants, Arnoud van der Laarse, Ernst E. van der Wall, J. Wouter Jukema

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Abstract

Background

Patients with metabolic syndrome have an increased risk of cardiovascular events. The number of patients with metabolic syndrome is rapidly growing and they often need revascularization. However, only limited data are available on the effect of metabolic syndrome on restenosis in patients undergoing percuta neous coronary intervention (PCI).

Methods

In order to assess the role of metabolic syndrome in the development of reste nosis, we performed an analysis in a population of patients from the GENetic DEterminants of Restenosis (GENDER) study. The GENDER project, a multi center prospective study, included consecutive patients after successful PCI and was designed to study the predictive value of various genetic and other risk fac tors for subsequent clinical restenosis defined as target vessel revascularization (TVR) or combined endpoint of death, myocardial infarction and TVR. This subpopulation of GENDER consisted of 901 patients, of whom 448 (49.7%) had metabolic syndrome.

Results

On multivariable Cox regression, controlling for age, sex, previous myocardial infarction, stent length, current smoking and statin therapy there was no as sociation between increased risk for TVR (HR 1.03, 95% CI 0.68- 1.57) or the combined endpoint (HR 1.05, 95% CI 0.71 - 1.55) and presence of metabolic syndrome.

Conclusions

This study demonstrates that metabolic syndrome is not associated with TVR or the combined endpoint after PCI. Furthermore, accumulating characteristics of metabolic syndrome were neither associated with increased risk of TVR nor with the combined endpoint. Thus, PCI has equal beneficial results in patients with or without metabolic syndrome. This is important information in light of the pandemic proportion of metabolic syndrome the medical community is go ing to be faced with.

Introduction

The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) has stressed the importance of targeting prevention strategies for in dividuals with metabolic syndrome.[1;2] Moreover, metabolic syndrome was re cently found to be a predictor of 4-year cardiovascular risk only when associated with significant angiographic CAD.[3] However, the consequences of metabolic syndrome on clinical restenosis in patients who undergo percutaneous coronary intervention (PCI) and coronary stent placement, remains unknown.
Clinical restenosis remains a problem after PCI. Diabetes and insulin resistance have already been shown to be independent predictors of early restenosis after coronary stenting.[4-6] However, only limited information is available on meta bolic syndrome, as a whole and its components, with regard to clinical reste nosis. The aim of our study was to examine whether the presence of metabolic syndrome constitutes a risk factor for clinical restenosis.

Methods

Study design

The GENetic DEterminants of Restenosis project (GENDER) was designed as a prospective multicenter follow-up study to evaluate various genetic risk fac tors in association with clinical restenosis. The study design has been reported previously.[7] In brief, patients were eligible for inclusion if they were successfully treated for stable angina, non-ST elevation acute coronary syndromes or silent ischemia with PCI. Patients treated for acute ST elevation myocardial infarction (MI) were excluded. The overall inclusion period lasted from March 1999 until June 2001. In order to study the effect of metabolic syndrome as a risk factor for restenosis, we determined the lipid profile (serum triglycerides, serum total cholesterol, serum HDL-cholesterol) and fasting serum glucose, in a subpopula tion of patients of whom plasma was collected. The study protocol conforms to the Declaration of Helsinki and was approved by the ethics committees of the participating institutions. Written informed consent was obtained from each participant before the PCI procedure.

Angioplasty and stenting procedure

Balloon angioplasty and intracoronary stenting were performed with standard

techniques using the radial or femoral approach. The use of intracoronary stents and additional medication, such as glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. If a stent was implanted, patients received either ti clopidin or clopidigrel for at least one month following the procedure, depend ing on local practice. Intracoronary brachytherapy or drug-eluting stents were not used in this study. The total length of the stented segment and the minimal diameter of the stents were calculated per patient.

Data collection

At inclusion, medical history, symptoms of cardiovascular disease and risk fac tors, current and former smoking habits, presence of vascular diseases in first de gree relatives and information about the use of current medical treatment of the patients were collected. Furthermore, patients had a physical examination that included measurements of body weight, height and blood pressure. Laboratory tests were performed to determine the lipid profile (serum triglycerides, serum total cholesterol, serum HDL-cholesterol) and fasting serum glucose. Blood was drawn before the PCI-procedure. Cholesterol, glucose and triglycerides concen trations in serum were measured with a fully automated Hitachi 747 (Hitachi, Tokyo, Japan). HDL cholesterol was determined with a turbidimetric assay on a Hitachi 911 and insulin was measured with an immunoradiometric assay (Bio source, Nivelles, Belgium). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Follow-up and study endpoints

Patients were followed for at least nine months. Primary endpoint was the inci dence of target vessel revascularisation (TVR) either by repeat PCI or CABG, which we considered as clinical restenosis. The secondary combined endpoint was defined as death presumably from cardiac causes, MI not attributable to an other coronary artery than the target vessel, and TVR. An independent clinical events committee of experienced cardiologists adjudicated the clinical events. The committee members did not review patients treated in their own center. Events occurring within one month were classified and analysed separately, since these events are more likely attributable to sub-acute stent thrombosis or oc cluding dissections and not to restenosis.[7]

Definitions

Patients were defined as having metabolic syndrome when having, 3 or more of the following criteria; 1.) Triglycerides ≥ 1.7mmol/L (150mg/dL) 2.) HDL choles terol: Men < 1.04mmol/L (40mg/dL), Women < 1.3mmol/L (50mg/dL) 3.) Systolic

blood pressure (BP) ≥130 mmHg, and/or diastolic BP ≥85 mmHg 4.) Obesity was defined by BMI of >28.8 kg/m2. This cutoff was equivalent to a waist circum ference of 102 cm in a cross-sectional study and similar to BMI value (28.2 kg/ m2) calculated in a regression of BMI on waist in a large population of Scottish men.[8;9] and 5.) Fasting glucose ≥ 5.55 mmol/L (100mg/dL), which was recently established in the American Diabetes Association, above which persons have ei ther pre-diabetes (impaired fasting glucose) or diabetes, and suggested this new cut point for identifying the lower boundary to define an elevated glucose as one criterion for the metabolic syndrome.[1;2;10]

Statistical methods

All data are presented as mean ± standard deviation, unless stated otherwise. Time to first clinical event was compared between (sub)groups of patients with the log-rank test. Prognostic value of clinical and procedural variables was as sessed with Cox' proportional hazards model. All event rates were calculated from Kaplan-Meier survival analysis. We used multivariable Cox regression models to examine the association of metabolic syndrome with risk of TVR and the combined endpoint after adjustment for potentially confounding factors. The covariates included in the baseline multivariable model were age, sex, pre vious MI, stent length, current smoking, and statin therapy. Subgroup analysis was performed in subgroups of patients with or without diabetes mellitus and for men and women. A two-sided value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS for Windows version 11.5 (SPSS Inc, Chigago, IL, US).

Results

The GENDER-study included 3,146 unselected consecutive patients, treated with successful PCI. Two of the four participating centers (Leiden University Medical Center and Academic Hospital Maastricht) collected systemically extra blood samples to perform additional laboratory measurements to examine other predictors of restenosis. In total 901 patients had sufficient data to establish absence or presence of metabolic syndrome. Patients were followed for at least nine months except when a coronary event occurred. The overall follow-up of the patients had a median duration of 9.6 months (interquartile range 3.9). Of these patients, 448 (49.7%) had metabolic syndrome (≥ 3 of the 5 characteristics). Of the 5 characteristics used to define metabolic syndrome, the prevalence of increased blood pressure was highest (85.5%), whereas increased BMI was the

least prevalent characteristic (46.2%) (Table 1).

Table 1. Prevalence of Metabolic Syndrome Characteristics

Metabolic Syndrome Characteristic	Metabolic Syndrome Absent N= 453 (50.3%)	Metabolic Syndrome Present N=448 (49.7%)
BMI >28.8 kg/m^2	37 (8.2%)	207 (46.2%)
Triglycerides ≥ 1.7 mmol/L	128 (28.3%)	370 (82.6%)
HDL cholesterol < 1.04 mmol/L men and < 1.3 mmol/L women	128 (28.3%)	324 (72.3%)
Systolic BP ≥130 and diastolic BP ≥85 mm Hg	273 (60.3%)	383 (85.5%)
Fasting glucose ≥ 5.55 mmol/L	115 (25.4%)	329 (73.4%)

BMI; body mass index, BP; blood pressure

The most common combination of metabolic abnormalities in the 448 met abolic syndrome patients (309 patients, 69%) was high triglyceride levels and high blood pressure. The presence of one or more components of the metabolic syndrome was common in both sexes; 16.3% had one component, 29.6% had two components, 26.9% had three components, 15.9% had four components and 7.0% had all five components (Table 4). Among the patients with diabetes in our cohort (n=140), 5% had one component, 17.9% had two components, 32.9% had three components, 26.4% had four components and 17.9% had all five compo nents.

As expected, patients in whom metabolic syndrome was present were more like ly to be younger, to have diabetes mellitus and increased BMI (Table 2). There was no significant difference in the number of coronary stents placed between patients with metabolic syndrome (83%) as opposed to those without (80%). Patients with metabolic syndrome received more statin therapy (p=0.014) and were more likely to be insulin dependent (p=0.003). As regards biochemical data, patients with metabolic syndrome had significantly higher erythrocyte sedimen tation rates (ESR) and insulin levels at baseline.

On multivariable Cox regression there was an expected trend towards increased risk of death and MI in patients with metabolic syndrome compared to those without, however the results were not statistically significant (Table 3). Inter

estingly, there was no association whatsoever, between increased risk for TVR (Hazard Ratio [HR] 1.03, 95% CI 0.68- 1.57) or the combined endpoint (HR 1.05, 95% CI 0.71 – 1.55) and presence of metabolic syndrome. The Kaplan-Meier curves are presented in Figure 1.

Table 2. Baseline Characteristics by Metabolic Syndrome Status (N=901)

	Metabolic syndrome		
	Absent	**Present**	***P*-value***
Baseline Characteristics:	**N=453**	**N=448**	
Age, (y± SD)	63 (±10)	61 (±11)	0.003
BMI (kg/m^2 ± SD)	25.4 (±3.0)	28.7 (±4.1)	<0.001
Female Sex (%)	127 (28)	131 (29)	0.69
Diabetes Mellitus (%)	32 (7)	108 (24)	<0.001
Current Smoking (%)	80 (18)	94 (21)	0.21
Family History of MI (%)	150 (33)	159 (36)	0.45
Previous MI (%)	174 (38)	183 (41)	0.45
Previous PTCA (%)	77 (17)	86 (19)	0.39
Previous CABG (%)	59 (13)	63 (14)	0.64
Baseline Medication:			
Beta-blocker (%)	345 (76)	363 (81)	0.08
Ca-antagonist (%)	199 (43)	221 (49)	0.10
Aspirin/ASA (%)	369 (82)	370 (83)	0.66
ACE Inhibitiors (%)	112 (25)	107 (24)	0.77
Insulin Therapy (%)	13 (3)	32 (7)	0.003
Statins (%)	231 (51)	265 (59)	0.014
Angiographic Data:			
Stent placement (%)	376 (80)	373 (83)	0.92
Total stent length (mm± SD)	23.4 (±18.5)	23.0 (±19.0)	0.53
Biochemical data:			
ESR** (mm/h, IQR)	10.0 (15)	12.0 (20)	0.006
Total cholesterol (mmol/L, ±SD)	4.91 (±1.05)	5.01 (±1.12)	0.32
Fibrinogen (g/l, ± SD)	3.73 (±1.62)	3.82 (±1.19)	0.22
Insulin** (mU/l, IQR)	12 (9)	20 (20)	<0.001

** P value of the nonparametric Mann Whitney test, or chi square test*

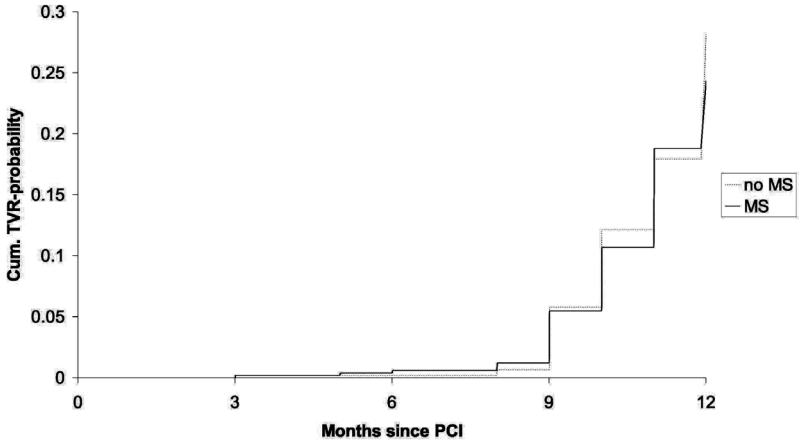
*** ESR and insulin are presented as median with interquartile range IQR*

Table 3. Hazard Ratios of cardiovascular events according to presence of metabolic syndrome (n=901)

	Metabolic Syndrome Absent N (%)	Metabolic Syndrome Present N (%)	Hazard Ratio* (95% CI)
Death of cardiac origin	4 (0.9)	8 (1.8)	2.52 (0.75 – 8.48)
Death from other causes	3 (0.7)	3 (0.7)	1.12 (0.22 – 5.72)
Death all causes	7 (2)	11 (3)	1.97 (0.76 – 5.10)
MI	2 (0.4)	6 (1.3)	2.72 (0.54 – 13.63)
TVR	45 (9.9)	47 (10.5)	1.03 (0.68-1.57)
Combined endpoint **	51 (11.3)	54 (12.1)	1.05 (0.71-1.55)

**Adjusted for age, sex, previous MI, stent length, current smoking, and statin therapy*
*** Combined endpoint was defined as death presumably from cardiac causes, MI not attrib utable to another coronary artery than the target vessel, and TVR either by repeat PCI or CABG*

Figure 1. Kaplan-Meier curve of the cumulative probability of combined endpoint



Combined endpoint was defined as death presumably from cardiac causes, MI not attribut able to another coronary artery than the target vessel, and TVR either by repeat PCI or CABG.

In the subgroup of patients with 0,1,2,3,4 or 5 metabolic syndrome defining char acteristics, the incidence of TVR was 5, 13, 27, 27, 13, and 7, respectively (p=0.77) (Table 4). On multivariable Cox regression there was no significant increase in risk of TVR in patients with metabolic syndrome or any number of its compo nents compared to patients without metabolic syndrome or with no character istics of metabolic syndrome.

Table 4. Hazard Ratios of TVR and clinical restenosis according to presence of accumulating characteristics of metabolic syndrome

Number of Metabolic Syndrome Character-istics	Patients 901 (%)	TVR 92 (%)	Hazard Ratio* (95% CI)	Combined Endpoint ** 105 (%)	Hazard Ratio * (95% CI)
0	39 (4.3)	5 (5.4)	1 (reference)	6 (5.7)	1 (reference)
1	147 (16.3)	13 (14.1)	0.61 (0.22-1.71)	14 (13.3)	0.55 (0.21-1.44)
2	267 (29.6)	27 (29.3)	0.68 (0.26-1.76)	31 (29.5)	0.66 (0.27-1.57)
3	242 (26.9)	27 (29.3)	0.79 (0.30-2.05)	32 (30.5)	0.78 (0.33-1.87)
4	143 (15.9)	13 (14.1)	0.52 (0.19-1.46	14 (13.3)	0.47 (0.18-1.23)
5	63 (7.0)	7 (7.6)	0.79 (0.25-2.50)	8 (7.6)	0.76 (0.26-2.18).
Overall ANOVA		*P*=0.77		*P*=0.81	

**Adjusted for age, sex, previous MI, stent length, current smoking, and statin therapy*
*** Combined endpoint was defined as death presumably from cardiac causes, MI not attrib utable to another coronary artery than the target vessel, and TVR either by repeat PCI or CABG*

We performed subgroup analysis to evaluate risk analysis of metabolic syndrome in subgroups of patients with or without diabetes mellitus. The adjusted HR for TVR was 2.83 (95% CI 0.62-12.69, p=0.17) in the subgroup of patients with diabetes, whereas HR was 0.84 (95% CI 0.52-1.35, p=0.47) in the group of pa tients without diabetes mellitus. This difference in HR was however not signifi cant (p=0.15). The same result was obtained for the combined endpoint (overall p=0.12).

When we analyzed the difference in TVR risk for men in comparison to women we found that the HR for TVR was 0.99 (95% CI: 0.61 - 1.58, p = 0.99) for men and 0.87 (95% CI: 0.42 - 1.84, p = 0.72) for women. This difference in HR was also not significant (p = 0.85).

Discussion

Previously, patients with metabolic syndrome have been shown to have higher prevalence of angiographic coronary artery disease (CAD) and to have higher cardiovascular risk only when associated with significant angiographic CAD.[3;5;11] However, the effect of metabolic syndrome, present in a rapidly growing patient population, on clinical restenosis in patients undergoing PCI and coronary stent placement was thus far, unknown.

The results of our prospective follow-up study of patients who underwent PCI, demonstrate that metabolic syndrome is neither associated with TVR nor with the combined endpoint. Furthermore, accumulating characteristics of meta bolic syndrome were neither associated with increased risk of TVR nor with combined endpoint. Similar to a previous study showing increased risk for car diovascular disease [3] in patients with metabolic syndrome compared to those without, we observed an expected trend towards increased risk of death and MI; however the results were not statistically significant, due to low number of cases death and MI on follow-up.

Of the various components of metabolic syndrome, the presence of diabetes has been shown to be associated with increased risk for restenosis after PCI and coronary stent placement.[12] However, a recent meta-analysis reported that, although the published literature suggests that diabetes is a risk factor for reste nosis in patients after PCI and coronary stent placement, this effect is overesti mated since this effect is partly related to older age of the patients, an important factor for restenosis.[13] In our study, the mean age of our population with meta bolic syndrome was lower than those without. Since age has been found to be a confounding factor of metabolic syndrome, we have controlled for age in the multivariable analysis, however a residual protective effect of younger age in the patients with metabolic syndrome cannot be fully excluded.

Furthermore, in the recent meta-analysis [13], rates of restenosis were higher in patients treated with insulin, which in turn may be a marker for disease duration and severity.[14;15] However, in our study despite an increased frequency of insulin therapy among our patients with metabolic syndrome, there was no difference in risk of clinical restenosis, between patients with metabolic syndrome with or without insulin therapy.

Previously we have reported that in the GENDER population diabetes is indeed an independent predictor for clinical restenosis.[7] However, in the present study metabolic syndrome did not seem to have similar risk for restenosis. One of the reasons for this could be that since presence of diabetes is only one of the three

out of five criteria used to define metabolic syndrome and only 24% of the pa tients with metabolic syndrome had overt diabetes in our population. Moreover our reference group or the group without metabolic syndrome also had 7% of patients with diabetes, could have further minimized any hazard ratio conferred by diabetes in the group with metabolic syndrome. Therefore, we would like to put the hypothesis forward that although presence of diabetes along with old age is a risk factor for restenosis, presence of metabolic syndrome per se is not associated with increased risk of clinical restenosis.

Limitations of the study

One of the limitations of our study is that we did not have waist circumference as per criteria of ATP-III. We therefore substituted waist circumference with variable of obesity as defined by BMI of >28.8 kg/m^2, this cutoff was equivalent to a waist circumference of 102 cm in a cross-sectional study and similar to BMI value (28.2 kg/m^2) calculated in a regression of BMI on waist in a large popula tion of Scottish men.[8;9] Furthermore, we cannot exclude the possibility of some misclassification bias on the presence or absence of some of the components of metabolic syndrome due to effective pharmacological therapy at the time of diagnosis. Off note the presence or absence of statin therapy did not influence restenosis rates.

In conclusion the results of this prospective follow-up study of patients that underwent PCI demonstrate that metabolic syndrome is neither associated with TVR nor with the combined endpoint. Furthermore, accumulating characteris tics of metabolic syndrome were not associated with increased risk of TVR or the combined endpoint. Therefore, PCI is an option to treat symptomatic CAD as good in patients with metabolic syndrome as in patients without. This is im portant information in light of the pandemic proportion of metabolic syndrome the medical community is going to be faced with.

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