Presence of the Metabolic Syndrome Does Not Impair Coronary Collateral Vessel Formation in Patients With Documented Coronary Artery Disease

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OBJECTIVE — The metabolic syndrome confers an increased risk for cardiovascular morbidity and mortality. The presence of coronary collaterals may have beneficial effects during myocardial ischemia and may improve cardiovascular outcome in patients with coronary artery disease. Impaired collateral formation could be one of the reasons for the increased cardiovascular risk in patients with the metabolic syndrome. The aim of the present study was to determine the influence of the metabolic syndrome and insulin resistance on the presence of coronary collaterals.

RESEARCH DESIGNS AND METHODS — We conducted a cross-sectional study in 227 patients referred for elective percutaneous transluminal coronary angioplasty to the University Medical Centre Utrecht. The metabolic syndrome was diagnosed according to Adult Treatment Panel III, and homeostasis model assessment of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were used to quantify insulin resistance. Coronary collaterals were graded with Rentrop's classification. Rentrop grade ≥1 indicated the presence of collaterals. Results were adjusted for age, sex, and severity of coronary artery disease.

RESULTS — A total of 103 patients (45%) were diagnosed with the metabolic syndrome. There was no association between the metabolic syndrome and the presence of coronary collateral formation (odds ratio [OR] 1.2 [95% CI 0.7–2.0]). Also, the degree of insulin resistance was not related to the presence of coronary collaterals. The OR for HOMA-IR (highest versus lowest tertile) was 0.7 (0.3–1.5) and for QUICKI (lowest versus highest tertile) 0.8 (0.4–1.6).

CONCLUSIONS — The metabolic syndrome and insulin resistance are not related to the presence of coronary collaterals in patients with documented coronary artery disease.

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitive C-reactive protein; PTCA, percutaneous transluminal coronary angioplasty; QUICKI, quantitative insulin sensitivity check index; SMART, Second Manifestations of Arterial Disease.

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

The metabolic syndrome is a cluster of generally accepted cardiovascular risk factors such as impaired glucose metabolism, elevated blood pressure, dyslipidemia, and central obesity (1). Also, other often not routinely measured cardiovascular risk factors (e.g., inflammation, increased oxidative stress, increased small dense LDL cholesterol, impaired fibrinolysis, hypercoagulability, and hyperinsulinemia) cluster in this syndrome (2). The underlying pathophysiology is still not fully clarified, but insulin resistance is a major characteristic. Increased adipose tissue mass is involved in the development of insulin resistance by metabolic alterations such as changes in the production of cytokines (3,4).

The prevalence of the metabolic syndrome is high, amounting to 24% in an apparently healthy westernized population (5). In patients with manifest vascular disease, the prevalence is 46% (6). The number of subjects with the metabolic syndrome is likely to increase in the coming years due to the increased prevalence of obesity. Patients with the metabolic syndrome are at an increased risk for cardiovascular morbidity and mortality (7–12). Several studies report a two- to threefold increased risk (13–15). This increased risk can be at least partially explained by the risk factors clustering in the metabolic syndrome.

Well-developed coronary collaterals are associated with improved cardiovascular outcome in terms of limiting myocardial infarction size, prevention of ventricular aneurysm formation (16,17), and future ischemic events (18,19) in patients with coronary artery disease. Repetitive myocardial ischemia and increased shear stress are important determinants of coronary collateral development (20,21).

It could be hypothesized that impaired coronary collateral formation contributes to the increased cardiovascular risk in metabolic syndrome patients. Since adequate collateral formation has

been suggested to be critically dependent on endothelial function and nitric oxide (NO) bioavailability (22,23), endothelial dysfunction could be one of the potential mechanisms for the decreased presence of coronary collaterals. Abaci et al. (24) demonstrated a decreased presence of coronary collaterals in diabetic patients. However, this could not be confirmed by others (25–28). To our best knowledge, no information on coronary collaterals is available in patients with the metabolic syndrome.

Insulin resistance may be linked to endothelial dysfunction by several mechnisms, including inflammation (as reflected by elevated high-sensitive C-reactive protein [hs-CRP] plasma levels), disruption of insulin receptor signaling cascades, increased production of cytokines, and activation of the renin angiotensin system (29,30). Adiponectin, an adipocyte-derived protein, stimulates the production of NO in vascular endothelial cells in vitro (31), and hypoadiponectinemia is associated with insulin resistance (32,33).

The aim of the present study is to determine the relation of the metabolic syndrome and insulin resistance with coronary collateral formation in patients referred for elective percutaneous transluminal coronary angioplasty (PTCA).

RESEARCH DESIGN AND METHODS

Patients originated from the Second Manifestations of Arterial Disease (SMART) Study, an ongoing prospective cohort study at the University Medical Centre Utrecht designed to establish the prevalence of concomitant arterial diseases and risk factors for atherosclerosis in a high-risk population (34). The local ethics committee approved the study, and all participants gave their written informed consent. For the present cross-sectional study, based on a case-cohort study investigating determinants and prognostic value of coronary collateral formation, 227 patients referred for elective PTCA and included in the SMART study between 1 January 1998 and 8 July 2002 were enrolled.

At the time of enrollment, clinical information was obtained using a standardized health questionnaire for all patients. Height, body weight, waist circumference, and blood pressure were measured. Fasting blood was sampled to determine lipid, serum glucose, homocysteine, creatinine, adiponectin, hs-CRP, and insulin levels. Insulin was measured with an immunometric assay (Diagnostic Products, Los Angeles, CA), and adiponectin was measured with a quantitative enzyme immunoassay technique (R&D Systems, Minneapolis, MN). Two experienced observers, blinded to all patient characteristics, independently reviewed all pre-PTCA coronary angiograms. Rentrop's classification was used to determine the extent of collateralization (grade 0: no filling of collateral vessels; grade 1: filling of collateral vessels without any epicardial filling of the recipient artery; grade 2: partial epicardial filling by collateral vessels of the recipient artery; and grade 3: complete epicardial filling by collateral vessels of the recipient artery) (35). By visual assessment of the pre-PTCA coronary angiograms, severity of coronary artery disease was defined (single, two, or three vessel disease) as the degree of the most severe stenosis (50–90, 90–99, or 100% stenosis). A ≥50% diameter reducing stenosis was regarded as significant (36).

Definitions

Metabolic syndrome was diagnosed according to the Adult Treatment Panel III criteria, including three or more of the following metabolic abnormalities: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), high blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic), hypertriglyceridemia (serum triglycerides ≥1.70 mmol/l [150 mg/dl]), low HDL cholesterol (serum HDL cholesterol <1.04 mmol/l [40 mg/dl] in men and <1.29 mmol/l [50 mg/dl] in women), and high fasting glucose (fasting serum glucose ≥6.1 mmol/l [110 mg/dl]) (1). Patients on glucose-lowering agents or antihypertensive medication were regarded as having high fasting glucose and high blood pressure, respectively. Waist circumference was not measured until 1 January 1999. If waist circumference was not available, a BMI cut point of 30 kg/m^2 was used as determinant for obesity (37). A fasting glucose ≥7.0 mmol/l in patients with no history of diabetes was considered as newly diagnosed diabetes. Established diabetes was defined as self-reported diabetes.

HOMA-IR and quantitative insulin sensitivity check index (QUICKI) were used as quantitative estimates of insulin resistance. HOMA-IR was calculated using the following formula: HOMA-IR = (fasting serum glucose × fasting serum insulin)/22.5 (38); QUICKI was calculated according to the following equation: 1/(log fasting serum glucose + log fasting serum insulin) (39).

The presence of coronary collaterals was defined as a Rentrop score ≥1. Severity of coronary artery disease was categorized in two groups (single versus multivessel [including two- or three-vessel] disease). HOMA-IR and QUICKI were categorized in tertiles.

Data analyses

Differences between patients with and without metabolic syndrome were tested with χ^2 (categorical variables), unpaired *t* test (continuous normal distributed variables), or Mann-Whitney *U* (continuous skewed variables).

The Rentrop score was dichotomized (score 0 indicating the absence and score ≥1 indicating the presence of coronary collaterals). The relation between the presence or absence of coronary collaterals and metabolic syndrome was quantified using the binary logistic regression model. Subsequently, this association was adjusted for age, sex, and severity of coronary artery disease. For obvious reasons, we did not adjust for factors included in the definition of the metabolic syndrome. These analyses were also performed with the values of HOMA-IR (categorized in tertiles), QUICKI (categorized in tertiles), and the number of components of the metabolic syndrome as independent variables, respectively, and the presence of collaterals as the dependent variable. HOMA-IR and QUICKI were only calculated in patients who were not on glucose-lowering agents. hs-CRP values >15 mg/l were excludeh from the analyses since they may indicate the presence of an active inflammatory disease. We also investigated the relationship between the separate continuous components of the metabolic syndrome and the presence of coronary collaterals. Regarding the association between blood pressure and coronary collateral formation and glucose levels and coronary collateral formation, patients with antihypertensive drugs and glucose-lowering agents were excluded.

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 10.1 (SPSS, Chicago, IL).

Table 1—*Baseline characteristics of the study population*

	Metabolic syndrome	
	No	Yes
n	124	103
Male sex	88	77
Age (years)	58 ± 10	58 ± 8
BMI (kg/m^2)	26 ± 3	29 ± 3
Smoking*	81	77
Total cholesterol (mmol/l)	5.0 (4.4–5.7)	5.4 (4.7–6.2)
Adiponectin (mg/l)	5.3 (3.7–7.5)	4.1 (3.0–6.4)
hs-CRP (mg/l)†	2.0 (1.1–3.9)	3.2 (2.0–6.6)
Creatinine clearance (Cockcroft) (ml/min)	79 ± 17	85 ± 17
Fasting serum insulin (mIU/l)‡	15 (9–24)	19 (11–35)
Diabetes§	7	40
Glucose-lowering agents	3	19
Antihypertensive drugs	21	44
Lipid-lowering agents	48	56
Parameters of coronary artery disease		
Severity of coronary vessel disease‖		
One-vessel disease	63	53
Two-vessel disease	30	36
Three-vessel disease	7	11
Degree of most severe lesion‖		
50–90% stenosis	65	59
90–99% stenosis	18	17
100% stenosis	17	24
Duration angina pectoris until PTCA (years)	3 ± 5	3 ± 5
Previous myocardial infarction	39	50
Previous PTCA and/or coronary artery bypass grafting	29	31
Components of metabolic syndrome		
Waist circumference (cm)	95 ± 9	101 ± 8
Systolic blood pressure (mmHg)	132 ± 21	140 ± 18
Diastolic blood pressure (mmHg)	76 ± 10	80 ± 9
HDL cholesterol (mmol/l)	1.15 (0.96–1.32)	0.93 (0.82–1.10)
Triglycerides (mmol/l)	1.38 (1.06–1.63)	2.25 (1.78–3.22)
Fasting serum glucose (mmol/l)	5.6 (5.2–5.9)	6.5 (5.7–8.1)

Data are means ± SD, median (interquartiles range), or percentages. *Still smoking, recently stopped smoking, or previously smoking; †plasma values >15 mg/l excluded from analyses; ‡patients on glucose-lowering agents excluded from analyses; §fasting serum glucose ≥7.0 mmol/l or self-reported diabetes; ‖according to pre-PTCA angiograms.

Table 2—*Relation of the metabolic syndrome, the number of components (according to Adult Treatment Panel III criteria), and the presence of coronary collaterals according to Rentrop's classification*

	Rentrop grade 0	Rentrop grade ≥1
Metabolic syndrome		
No	80 (65)	44 (35)
Yes	61 (59)	42 (41)
Number of components		
Zero	9 (64)	5 (36)
One	31 (66)	16 (34)
Two	40 (63)	23 (37)
Three	29 (57)	22 (43)
Four	18 (58)	13 (42)
Five	14 (67)	7 (33)

Data are *n* (%).

RESULTS — Table 1 describes the baseline characteristics of the study population according to the presence of the metabolic syndrome: 103 patients (45%) with the metabolic syndrome and 124 patients without (55%). In 58 patients, waist circumference was not available. Substituting a BMI cut point of 30 kg/m^2 as a determinant for obesity classified only two more patients with the metabolic syndrome (103 vs. 101 patients when BMI was not substituted). In one patient, both waist circumference and BMI were missing. Age and smoking habits were equally distributed. Patients with the metabolic syndrome had a higher creatinine clearance compared with non–metabolic syndrome patients (85 vs. 79 ml/min). Metabolic syndrome patients had higher hs-CRP plasma levels (3.2 vs. 2.0 mg/l) and lower adiponectin levels (4.1 vs. 5.3 mg/l) compared with their non–metabolic syndrome counterparts. Severity of coronary artery disease was classified as single-vessel disease in 53% and as multivessel disease in 47% of the metabolic syndrome patients, versus 63 and 37% in non–metabolic syndrome patients, respectively. As expected, all five diagnostic parameters of the metabolic syndrome were more common in patients with the metabolic syndrome than in patients without. Rentrop grade ≥1 was present in 41% of the metabolic syndrome patients and in 35% of the non–metabolic syndrome patients. Coronary collaterals were present in 36% of the patients without any components of the metabolic syndrome, in 34% of the patients with one component, in 37% of the patients with two components, in 43% of the patients with three components, in 42% of the patients with four components, and in 33% of the patients with all components of the metabolic syndrome (Table 2).

No difference was found in the presence of coronary collaterals between patients with and without the metabolic syndrome (crude OR 1.3 [95% CI 0.7–2.1]). Age, sex, and the severity of coronary artery disease did not influence the relationship between the metabolic syndrome and coronary collaterals (adjusted OR 1.2 [0.7–2.0]). The number of single components of the metabolic syndrome similarly showed no association with coronary collateral formation. When patients with established diabetes were excluded from analyses, results remained the same (data not shown). Also, no significant associations were found between the separate continuous components of the

Table 3—*Relation of the metabolic syndrome, the individual components (according to the Adult Treatment Panel III criteria), and the presence of coronary collaterals*

	Crude	Adjusted for age and sex	Adjusted for age, sex, and severity of coronary artery disease*
Metabolic syndrome	1.3 (0.7–2.1)	1.3 (0.8–2.3)	1.2 (0.7–2.0)
Number of components			
Zero	Reference	Reference	Reference
One	0.9 (0.3–3.2)	0.9 (0.3–3.1)	1.1 (0.3–4.1)
Two	1.0 (0.3–3.5)	1.0 (0.3–3.5)	1.2 (0.3–4.1)
Three	1.4 (0.4–4.7)	1.4 (0.4–4.8)	1.5 (0.4–5.3)
Four	1.3 (0.4–4.8)	1.4 (0.4–5.1)	1.3 (0.3–4.9)
Five	0.9 (0.2–3.7)	1.0 (0.2–4.0)	1.0 (0.2–4.3)
Individual components†			
Waist circumference (cm)	1.02 (0.99–1.06)	1.02 (0.99–1.06)	1.02 (0.98–1.06)
Systolic blood pressure (mmHg)‡	0.99 (0.98–1.01)	0.99 (0.97–1.01)	0.99 (0.97–1.01)
Diastolic blood pressure (mmHg)‡	0.98 (0.94–1.01)	0.98 (0.94–1.01)	0.98 (0.94–1.01)
HDL cholesterol (mmol/l)	1.05 (0.38–2.86)	1.34 (0.45–4.01)	1.53 (0.50–4.71)
Triglycerides (mmol/l)	1.09 (0.91–1.30)	1.09 (0.90–1.33)	1.06 (0.91–1.23)
Fasting serum glucose (mmol/l)§	1.09 (0.88–1.36)	1.10 (0.88–1.36)	1.06 (0.85–1.33)

Data are OR (95% CI). *According to pre-PTCA angiograms (single- versus multivessel disease); †continuously; ‡patients with antihypertensive drugs excluded from analyses; §patients on glucose-lowering agents excluded from analyses.

metabolic syndrome and the presence of coronary collaterals (Table 3).

In Table 4, it is shown that quantitative estimates of insulin resistance are not associated with the presence of coronary collaterals. OR for HOMA-IR (highest versus lowest tertile) was 0.7 (95% CI 0.3–1.5) and for QUICKI (lowest versus highest tertile) 0.8 (0.4–1.6), after adjustment for age, sex, and severity of coronary artery disease. Additional analyses were performed after dichotomizing the Rentrop score in a more functional way (Rentrop score 0–1 vs. 2–3). Results essentially remained the same in comparison with analyses with Rentrop score 0 vs. 1–3 (data not shown).

CONCLUSIONS — The metabolic syndrome is associated with an increased risk for cardiovascular morbidity and mortality (7–15). Impaired coronary collateral formation has been reported in diabetes and may also contribute to the increased cardiovascular risk in metabolic syndrome patients. However, in the present study, we could not detect a relation between the metabolic syndrome and the presence of coronary collaterals in patients referred for elective PTCA. Moreover, no association was also found between insulin resistance and coronary collaterals.

The presence of coronary collaterals can be regarded as a beneficial response given an equal level of coronary atherosclerosis. Our results were adjusted for the severity of coronary artery disease to account for the fact that repetitive myocardial ischemia is an important determinant for collateral development.

To our best knowledge, this is the first clinical study examining the association between the metabolic syndrome (according to the Adult Treatment Panel III criteria) and the presence of coronary collaterals. There are several studies with contradictory findings on coronary collateralization in diabetic patients, probably due to differences in both the used definition of coronary collateral formation and the adjustment for the severity of coronary artery disease. In their angiographic study, Abaci et al. (24) showed that diabetic patients developed a less extensive coronary collateral circulation compared with nondiabetic patients. Endothelial dysfunction and blunted NO production, both associated with diabetes, were suggested to underlie this decreased collateralization. A recent study (28) found no difference in coronary collateral vessel formation between diabetic and nondiabetic patients using Rentrop's classification.

In an insulin-resistant state, hyperinsulinemia is associated with endothelial dysfunction by the release of the potent vasoconstrictor endothelin. Also, the increased production of cytokines, low-grade inflammation, defects in insulin signaling pathways, activation of the renin angiotensin system, and increased oxidative stress, all of which are associated with insulin resistance, could contribute to endothelial dysfunction (30). However, we showed that in patients referred for PTCA, the metabolic syndrome and insulin resistance are not associated with

Table 4—*Relation of quantitative estimates of insulin resistance (HOMA-IR and QUICKI) and the presence of coronary collaterals

	Crude	Adjusted for age and sex	Adjusted for age, sex, and severity of coronary artery disease†
HOMA-IR tertiles			
1	Reference	Reference	Reference
2	1.0 (0.5–2.0)	1.0 (0.5–2.1)	0.8 (0.4–1.8)
3	0.8 (0.4–1.7)	0.8 (0.4–1.7)	0.7 (0.3–1.5)
QUICKI tertiles			
1	0.9 (0.4–1.8)	0.9 (0.4–1.8)	0.8 (0.4–1.6)
2	1.0 (0.5–2.1)	1.1 (0.5–2.2)	0.8 (0.4–1.8)
3	Reference	Reference	Reference

Data are OR (95% CI). *Patients on glucose-lowering agents excluded from analyses; †according to pre-PTCA angiograms (single versus multivessel disease).

impaired coronary collateral formation. This may be due to several reasons. Firstly, we studied patients with advanced coronary artery disease. These patients may already have an impaired endothelial function to such an extent that the influence of insulin resistance on endothelial function could be neglected. Despite the fact that patients with the metabolic syndrome have significantly higher plasma levels of hs-CRP (3.2 vs. 2.0 mg/l, $P < 0.001$) and significantly lower plasma levels of adiponectin (4.1 vs. 5.3 mg/l, $P = 0.001$) (hs-CRP positively [40] and adiponectin negatively [41–43] associated with endothelial dysfunction), compared with non–metabolic syndrome patients, we did not find a difference in coronary collateralization. Secondly, vasoactive drugs, such as ACE inhibitors, angiotensin receptor blockers, and statins, could have positive effects on endothelial function (44–46). Moreover, statin use has been shown to be associated with enhanced collateralization in patients with documented coronary artery disease (47). Although the use of lipid-lowering agents was equally distributed in our study population, patients with the metabolic syndrome use ACE inhibitors or angiotensin receptor blockers significantly more often than patients without the metabolic syndrome (28 vs. 11%, $P = 0.001$). This could have ameliorated the endothelial dysfunction in metabolic syndrome patients. However, in the present study, we did not find a significant association between the use of ACE inhibitors or angiotensin receptor blockers and coronary collateralization (data not shown).

Finally, the technique used to visualize coronary collaterals could only identify blood vessels with diameters >100 μm. With this technique, contrary to myocardial contrast echocardiography, intramural collaterals also cannot be demonstrated, so coronary collateral blood flow can only be semiquantitatively assessed. It may be possible that patients with the metabolic syndrome have an impaired formation of collateral vessels with a diameter <100 μm or intramural situated collaterals. In addition to coronary angiography to determine coronary collateral development, several studies use intracoronary pressure and/or flow velocity assessments. Although this quantitative assessment of coronary collaterals is considered superior to the angiographic grading method used in this study (48–50), a major limitation of this technique is that it can only be performed during angioplasty, which restricts its applicability to a limited population. To investigate the influence of the metabolic syndrome on coronary collateral development in subjects without coronary artery disease, noninvasive imaging techniques for coronary collateral assessment should be developed.

We conclude that there is no significant association between the metabolic syndrome or insulin resistance and the presence of coronary collaterals in patients with documented coronary artery disease.

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APPENDIX— Participants of the SMART Study group are as follows: A. Algra; Y.v.d.G., D.E.G., G.E.H.M. Rutten, Julius Centre for Health Sciences and Primary Care; J.D. Banga, F.L.J.V., Department of Internal Medicine; B.C. Eikelboom, F.L. Moll, Department of Vascular Surgery; L.J. Kappelle, Department of Neurology; H.A. Koomans, Department of Nephrology; W.P.Th.M. Mali, Department of Radiology; P.P.Th.d.J., P.A. Doevendans, Department of Cardiology; University Medical Centre Utrecht, Utrecht, the Netherlands.

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