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

JOBIEN K. OLIJHOEK, MD[1]
JEROEN KOERSELMAN, MD[2]
PETER P.TH. DE JAEGERE, MD, PHD[3]
MARIANNE C. VERHAAR, MD, PHD[1]
DIEDERICK E. GROBBEE, MD, PHD[2]
YOLANDA VAN DER GRAAF, MD, PHD[2]
FRANK L.J. VISSEREN, MD, PHD[1]
FOR THE SMART STUDY GROUP*

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.

Diabetes Care **28:683–689, 2005**

From the [1]Department of Internal Medicine, Section of Vascular Medicine, University Medical Centre Utrecht, Utrecht, the Netherlands; the [2]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands; and the [3]Department of Cardiology, Erasmus Medical Centre Rotterdam, Rotterdam, the Netherlands.

Address correspondence and reprint requests to Jobien K. Olijhoek, MD, Department of Internal Medicine, Section of Vascular Medicine, University Medical Centre Utrecht, F02.126, Heidelberglaan 100, 3584 CX Utrecht, Netherlands. E-mail: j.k.olijhoek@amcutrecht.nl..

Received for publication 16 July 2004 and accepted in revised form 10 December 2004.

*A complete list of SMART Study group members can be found in the APPENDIX.

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.

Acknowledgments— The work presented in this report is part of a program grant from the Netherlands Organization for Scientific Research-Medical Sciences (NWO-MW Project no. 904-65-095). M.C.V. is supported by the Netherlands Organization for Scientific Research (NWO Grant no. 016-036-041).

The help of M. Edlinger for data coordination is greatly acknowledged.

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.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
2. Sakkinen PA, Wahl P, Cushman M, Lewis MR, Tracy RP: Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. *Am J Epidemiol* 152: 897–907, 2000
3. Jazet IM, Pijl H, Meinders AE: Adipose tissue as an endocrine organ: impact on insulin resistance. *Neth J Med* 61:194–212, 2003
4. Pittas AG, Joseph NA, Greenberg AS: Adipocytokines and insulin resistance. *J Clin Endocrinol Metab* 89:447–452, 2004
5. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. *JAMA* 287:356–359, 2002
6. Gorter P, Olijhoek JK, Graaf van der Y, Algra A, Rabelink AJ, Visseren FLJ, for the SMART Study Group: Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. *Atherosclerosis* 173:361–367, 2004
7. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 107:391–397, 2003
8. Onat A, Ceyhan K, Basar O, Erer B, Toprak S, Sansoy V: Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels: a prospective and cross-sectional evaluation. *Atherosclerosis* 165:285–292, 2002
9. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003
10. Trevisan M, Liu J, Bahsas FB, Menotti A: Syndrome X and mortality: a population-based study. Risk Factor and Life Expectancy Research Group. *Am J Epidemiol* 148: 958–966, 1998
11. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB: Clustering of metabolic factors and coronary heart disease. *Arch Intern Med* 159:1104–1109, 1999
12. Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL: The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. *Eur Heart J* 25:342–348, 2004
13. Alexander CM, Landsman PB, Teutsch SM, Haffner SM: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes* 52:1210–1214, 2003
14. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
15. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J,

Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288:2709–2716, 2002
16. Hirai T, Fujita M, Nakajima H, Asanoi H, Yamanishi K, Ohno A, Sasayama S: Importance of collateral circulation for prevention of left ventricular aneurysm formation in acute myocardial infarction. *Circulation* 79:791–796, 1989
17. Habib GB, Heibig J, Forman SA, Brown BG, Roberts R, Terrin ML, Bolli R: Influence of coronary collateral vessels on myocardial infarct size in humans: results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. *Circulation* 83:739–746, 1991
18. Pijls NH, Bech GJ, el Gamal MI, Bonnier HJ, De Bruyne B, van Gelder B, Michels HR, Koolen JJ: Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. *J Am Coll Cardiol* 25:1522–1528, 1995
19. Billinger M, Kloos P, Eberli FR, Windecker S, Meier B, Seiler C: Physiologically assessed coronary collateral flow and adverse cardiac ischemic events: a follow-up study in 403 patients with coronary artery disease. *J Am Coll Cardiol* 40:1545–1550, 2002
20. Koerselman J, van der Graaf Y, de Jaegere PP, Grobbee DE: Coronary collaterals: an important and underexposed aspect of coronary artery disease. *Circulation* 107: 2507–2511, 2003
21. Seiler C: The human coronary collateral circulation. *Heart* 89:1352–1357, 2003
22. Matsunaga T, Warltier DC, Weihrauch DW, Moniz M, Tessmer J, Chilian WM: Ischemia-induced coronary collateral growth is dependent on vascular endothelial growth factor and nitric oxide. *Circulation* 102:3098–3103, 2000
23. Murohara T, Asahara T, Silver M, Bauters C, Masuda H, Kalka C, Kearney M, Chen D, Symes JF, Fishman MC, Huang PL, Isner JM: Nitric oxide synthase modulates angiogenesis in response to tissue ischemia. *J Clin Invest* 101:2567–2578, 1998
24. Abaci A, Oguzhan A, Kahraman S, Eryol NK, Unal S, Arinc H, Ergin A: Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 99: 2239–2242, 1999
25. Melidonis A, Tournis S, Kouvaras G, Baltaretsou E, Hadanis S, Hajissavas I, Tsatsoulis A, Foussas S: Comparison of coronary collateral circulation in diabetic and nondiabetic patients suffering from coronary artery disease. *Clin Cardiol* 22: 465–471, 1999
26. Fujita M, Nakae I, Kihara Y, Hasegawa K, Nohara R, Ueda K, Tamaki S, Otsuka K, Sasayama S: Determinants of collateral development in patients with acute myocardial infarction. *Clin Cardiol* 22:595–599, 1999
27. Cohen M, Sherman W, Rentrop KP, Gorlin R: Determinants of collateral filling observed during sudden controlled coronary artery occlusion in human subjects. *J Am Coll Cardiol* 13:297–303, 1989
28. Werner GS, Richartz BM, Heinke S, Ferrari M, Figulla HR: Impaired acute collateral recruitment as a possible mechanism for increased cardiac adverse events in patients with diabetes mellitus. *Eur Heart J* 24:1134–1142, 2003
29. Baron AD: Vascular reactivity. *Am J Cardiol* 84:25J–27J, 1999
30. Wheatcroft SB, Williams IL, Shah AM, Kearney MT: Pathophysiological implications of insulin resistance on vascular endothelial function. *Diabet Med* 20:255–268, 2003
31. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ: Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 278: 45021–45026, 2003
32. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA: Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 86:1930–1935, 2001
33. Hulthe J, Hulten LM, Fagerberg B: Low adipocyte-derived plasma protein adiponectin concentrations are associated with the metabolic syndrome and small dense low-density lipoprotein particles: atherosclerosis and insulin resistance study. *Metabolism* 52:1612–1614, 2003
34. Simons PC, Algra A, van de Laak MF, Grobbee DE, van der Graaf Y: Second Manifestations of ARTerial disease (SMART) study: rationale and design. *Eur J Epidemiol* 15:773–781, 1999
35. Rentrop KP, Cohen M, Blanke H, Phillips RA: Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 5:587–592, 1985
36. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, Legako RD, Leon DF, Murray JA, Nissen SE, Pepine CJ, Watson RM, Ritchie JL, Gibbons RJ, Cheitlin MD, Gardner TJ, Garson A Jr, Russell RO Jr, Ryan TJ, Smith SC Jr: ACC/AHA Guidelines for Coronary Angiography: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 33:1756–1824, 1999
37. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
38. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
39. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ: Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab* 85:2402–2410, 2000
40. Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM: Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* 102:1000–1006, 2000
41. Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, Kumada M, Ohashi K, Okamoto Y, Nishizawa H, Kishida K, Maeda N, Nagasawa A, Kobayashi H, Hiraoka H, Komai N, Kaibe M, Rakugi H, Ogihara T, Matsuzawa Y: Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension* 42: 231–234, 2003
42. Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, Ueda S, Shimomura I, Funahashi T, Matsuzawa Y: Hypoadiponectinemia is closely linked to endothelial dysfunction in man. *J Clin Endocrinol Metab* 88:3236–3240, 2003
43. Tan KC, Xu A, Chow WS, Lam MC, Ai VH, Tam SC, Lam KS: Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. *J Clin Endocrinol Metab* 89:765–769, 2004
44. Lonn E: Antiatherosclerotic effects of ACE inhibitors: where are we now? *Am J Cardiovasc Drugs* 1:315–320, 2001
45. Hornig B, Landmesser U, Kohler C, Ahlersmann D, Spiekermann S, Christoph A, Tatge H, Drexler H: Comparative effect of ACE inhibition and angiotensin II type 1 receptor antagonism on bioavailability of nitric oxide in patients with coronary artery disease: role of superoxide dismutase. *Circulation* 103:799–805, 2001
46. Wolfrum S, Jensen KS, Liao JK: Endothelium-dependent effects of statins. *Arterioscler Thromb Vasc Biol* 23:729–736, 2003
47. Pourati I, Kimmelstiel C, Rand W, Karas RH: Statin use is associated with enhanced collateralization of severely diseased coronary arteries. *Am Heart J* 146: 876–881, 2003
48. Meier B, Luethy P, Finci L, Steffenino GD, Rutishauser W: Coronary wedge pressure in relation to spontaneously visible and

recruitable collaterals. *Circulation* 75:906–913, 1987
49. Seiler C, Fleisch M, Billinger M, Meier B: Simultaneous intracoronary velocity- and pressure-derived assessment of adenosine-induced collateral hemodynamics in patients with one- to two-vessel coronary artery disease. *J Am Coll Cardiol* 34:1985–1994, 1999
50. van Liebergen RA, Piek JJ, Koch KT, de Winter RJ, Schotborgh CE, Lie KI: Quantification of collateral flow in humans: a comparison of angiographic, electrocardiographic and hemodynamic variables. *J Am Coll Cardiol* 33:670–677, 1999