Metabolic syndrome in peripheral arterial disease: Relationship with severity of peripheral circulatory insufficiency, inflammatory status, and cardiovascular comorbidity

Gregorio Brevetti, MD, Vittorio Schiano, MD, Giusy Sirico, MD, Giuseppe Giugliano, MD, Eugenio Laurenzano, MD, and **Massimo Chiariello, MD,** *Naples, Italy*

Objective: **Metabolic syndrome is defined by the clustering in the same person of at least three risk factors such as hyperglycemia, hypertriglyceridemia, low levels of high-density lipoprotein, hypertension, and abdominal obesity. In patients with peripheral arterial disease (PAD), we investigated the prevalence of metabolic syndrome and its relationship with the severity of peripheral circulatory insufficiency, inflammatory status, and cardiovascular comorbidity.**

Methods: **The presence of metabolic syndrome was assessed in 154 consecutive PAD patients (115 men, 39 women). Inflammatory status was assessed by measuring serum levels of C-reactive protein (CRP).**

Results: **Metabolic syndrome was present in 51.9% (42.7 % in men, 74.3% in women, $P < .01$). Patients with an ankle/brachial index (ABI) <0.64 (median) were more likely to have metabolic syndrome than those with less severe PAD (63.9% vs 42.8%, $P < .02$). The association between a low ABI and metabolic syndrome was maintained after adjustment for age and sex (odds ratio [OR], 2.19; 95% confidence interval [CI], 1.03 to 4.68). Compared with PAD patients without metabolic syndrome, those with the syndrome had greater body mass index (28.2 [25.6; 29.8] kg/m^2 vs 26.1 [24.2; 27.7] kg/m^2, $P < .01$) and higher levels of CRP (3.9 [1.6; 7.6] mg/L vs 2.0 [1.1; 3.7] mg/L, $P < .02$). A previous myocardial infarction was documented in 58.2% of patients with and in 37.5% of those without metabolic syndrome ($P < .01$). At multivariate analysis, metabolic syndrome was significantly associated with previous myocardial infarction also after adjustment for ABI (OR, 2.15; 95% CI, 1.06 to 4.38).**

Conclusions: **Metabolic syndrome is present in >50% of PAD patients. The finding that well-established indicators of increased cardiovascular risk such as low ABI and increased CRP levels cluster with metabolic syndrome suggests that identification of this syndrome in these high-risk patients could indicate an even greater risk of cardiovascular events. (J Vasc Surg 2006;44:101-7.)**

Metabolic syndrome, which is defined by the clustering in the same person of at least three risk factors such as hyperglycemia, hypertriglyceridemia, low levels of high-density lipoprotein (HDL), hypertension, and abdominal obesity[1] confers an increased risk for coronary artery disease (CAD).[2-4] It is a widely shared belief that metabolic syndrome is a growing and pressing problem for society. Indeed, this condition is present in 9% to 22% of healthy subjects,[2,4,5] and its prevalence increases in high-risk populations.[6,7] In particular, a recent article reports that in patients with peripheral arterial disease (PAD), the prevalence of metabolic syndrome is as high as 58%, greater than that observed in subjects with coronary and cerebrovascular disease.[6] This finding may have relevant clinical implications, considering that PAD is highly prevalent in the adult populations,[8,9] is associated with elevated cardiovascular comorbidity,[10] and portends worse outcome.[11-13]

From the Department of Clinical Medicine and Cardiovascular and Immunological Sciences, University of Naples "Federico II."

Competition of interest: none.

Reprint requests: Gregorio Brevetti, MD, Via G. Iannelli 45/A, 80131 Napoli, Italy (e-mail: brevetti@unina.it).

CME article
0741-5214/$32.00

doi:10.1016/j.jvs.2006.02.048

Unfortunately, however, little is known about the relationship between metabolic syndrome and the clinical correlates of PAD. Accordingly, in a group of patients with PAD, we investigated the association of metabolic syndrome with (1) severity of atherosclerotic disease in the lower limbs, (2) risk factors not included in the definition of metabolic syndrome, and (3) cardiovascular comorbidity. The answers to these questions may help to clarify the mechanisms that favor the progression of the atherosclerotic disease in a population at high risk.

METHODS

Between July 2004 and October 2005, 154 consecutive patients (115 men, 39 women) entered the study with a qualifying diagnosis of PAD, defined as an ankle/brachial index (ABI) of <0.90 and, in diabetic patients with ABI >0.90, a history of typical claudication associated with one or more stenosis >50% of a lower-extremity artery. Of these, 142 were affected by intermittent claudication, and 12 had critical limb ischemia (pain at rest, or trophic lesions in the affected limb, or both). All participants gave their written informed consent to be in the study, which was approved by our institutional ethics committee.

Data collection. Historical and demographic information was collected at the first visit, after which all patients

Table I. Peripheral arterial disease severity, body mass index, plasma levels of highly sensitive C-reactive protein, and prevalence of previous myocardial infarction in patient groups*

Group A (n = 59)	*Group B (n = 16)*	*Group C (n = 21)*	*Group D (n = 58)*	P	
ABI <0.64 (%)	21 (35.5)	8 (50.0)	9 (42.8)	43 (74.1)	.008
Bilateral PAD (%)	36 (61.0)	12 (75.0)	14 (66.7)	43 (74.1)	NS
BMI (kg/m^2)	26.5 (24.2-27.9)	25.3 (23.7-26.8)	27.0 (25.1-29.5)	29.0 (25.9-30.0)	.002
Obesity (%)	5 (8.5)	1 (6.2)	3 (14.3)	15 (25.9)	.025
hs-CRP (mg/L)	2.2 (1.4-5.4)	1.9 (0.8-2.8)	3.4 (1.4-8.8)	4.0 (2.0-7.6)	.023
Previous MI (%)	23 (38.9)	5 (31.2)	10 (47.6)	36 (62.1)	.061

ABI, Ankle brachial index; *PAD,* peripheral arterial disease; *BMI,* body mass index; *hs-CRP,* highly sensitive C-reactive protein; *MI,* myocardial infarction; *NS,* not significant.

Data are presented as medians (interquartile ranges) and numbers (percentage).

*Group A, no diabetes and no metabolic syndrome; group B; patients with diabetes and no metabolic syndrome; group C, patients with metabolic syndrome and no diabetes; group D, patients with both metabolic syndrome and diabetes.

underwent a complete clinical and arterial evaluation, according to the routine protocol of our vascular laboratory. In brief, systolic pressure in the right and left posterior tibial arteries and the right brachial artery was measured twice with an echo color Doppler ultrasound scanning probe after the patients had been resting supine for 5 minutes. The average of the two measurements was used to evaluate ABI. The lower ABI value of the two legs was used for statistical analyses. Then, all patients underwent echo color Doppler ultrasound scanning of the abdominal aorta, the lower limbs, and the carotid arteries. Patients with no history of CAD underwent dipyridamole myocardial perfusion imaging to verify the presence or absence of ischemic heart disease.

Fasting venous blood was obtained with a nontraumatic venipuncture. Serum C-reactive protein (CRP) was determined with highly sensitive (hs) assay (Dade Behring Diagnostics, Marburg, Germany). Serum concentrations of triglycerides, total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and fasting glucose were measured with commercially available kits.

Diagnostic criteria. Metabolic syndrome was diagnosed according to the Adult Treatment Panel III (ATP III) criteria,[1] including three or more of the following abnormalities: abdominal obesity (waist circumference >102 cm in men; >88 cm in women), high blood pressure (≥130 mm Hg systolic or ≥85 mm Hg diastolic), hypertriglyceridemia (serum triglycerides ≥150 mg/dL), low levels of serum HDL cholesterol (<40 mg/dL in men; <50 mg/dL in women), and high fasting glucose (>110 mg/dL). Patients taking glucose-lowering agents or antihypertensive drugs were considered as having high fasting glucose and high blood pressure, respectively.

A history of cardiovascular disease was confirmed with hospital records documenting CAD (previous myocardial infarction, or positive coronary angiogram, or positive myocardial scintigram) and carotid vessel disease (previous stroke or ultrasonography-proved stenosis >50% in at least one carotid artery). Infrarenal abdominal aortic aneurysm (AAA) was defined by a lumen vessel dilation of ≥3 cm at the echo color Doppler ultrasound scanning.

Statistical analysis. Data are expressed as mean ± standard deviation (normally distributed) or median plus 25th and 75th percentile (nonnormally distributed). Differences between patients with and without metabolic syndrome were tested with unpaired *t* test (normally distributed), Mann-Whitney *U* test (nonnormally distributed), or χ^2 test (categoric variables).

For BMI and hs-CRP, which were nonnormally distributed, the comparison between patients with fewer than three components of the metabolic syndrome, those with three, and those with four components were made by Kruskal-Wallis test. Multivariate logistic regression analysis was used to assess the association between metabolic syndrome and other variables.

To verify whether diabetes alone was responsible for metabolic syndrome observations, we divided the study population into four groups: group A, patients with no metabolic syndrome and no diabetes; group B, patients with diabetes and no metabolic syndrome; group C, patients with metabolic syndrome and no diabetes; and group D, patients with both metabolic syndrome and diabetes. Group comparisons were made by Kruskal-Wallis test for BMI and CRP, and χ^2 test was used for categoric variables.

RESULTS

PAD severity and metabolic syndrome. Metabolic syndrome was present in 79 (51.9%) of 154 PAD patients included in this study, the prevalence being greater in women than in men (74.3% vs 42.7%, $P < .01$). In the 81 patients with an ABI <0.64 (median), the prevalence of the syndrome was significantly higher than in the 73 with an ABI >0.64 (63.9% vs 42.8%, $P = .016$). The association between low ABI and metabolic syndrome was also maintained after adjustment for age and sex (odds ratio [OR], 2.19; 95% confidence intervals [CI], 1.03 to 4.68; $P < .05$). These results remained substantially unmodified when four diabetic patients with abnormally elevated ABI were excluded from the analyses. As summarized in Table I, when patients were divided into the four groups, a significant difference was observed with respect to the prevalence

Table II. Baseline characteristics of the study population

	Metabolic syndrome		
	Yes (n = 79)	*No (n = 75)*	*P*
Cardiovascular risk factors not included in the metabolic syndrome			
Age (yr)	67.1 ± 9	67.5 ± 10	.774
Male/female	50/29	65/10	<.001
Total cholesterol (mg/dL)	196 ± 44	190 ± 38	.332
LDL cholesterol (mg/dL)	119 ± 31	121 ± 39	.756
Never smokers (%)	17 (21.5)	10 (13.3)	.174
Ex smokers (%)	33 (41.8)	37 (49.3)	.292
Current smokers (%)	29 (36.7)	28 (37.3)	.994
BMI (kg/m^2)	28.2 (25.6; 29.8)	26.1 (24.8; 27.7)	<.01
BMI ≥30 kg/m^2 (%)	18 (22.8)	6 (8.0)	<.01
CRP (mg/L)	3.9 (1.6; 7.6)	2.0 (1.1; 3.7)	.015
Components of metabolic syndrome			
High fasting glucose (%)	63 (79.7)	16 (21.3)	<.001
Glycemia (mg/dL)	147 ± 57	103 ± 33	<.001
Hypertension (%)	79 (100)	61 (81.3)	<.001
SBP (mm Hg)	140 ± 22	137 ± 23	.293
DBP (mm Hg)	80 ± 16	75 ± 12	.074
Hypertriglyceridemia (%)	52 (65.8)	3 (4.0)	<.001
Triglycerides (mmol/L)	182 ± 80	108 ± 28	<.001
Low HDL cholesterol (%)	48 (60.7)	4 (5.7)	<.001
HDL cholesterol (mmol/L)	43 ± 13	55 ± 15	<.001
Abdominal obesity (%)	63 (79.7)	14 (18.7)	<.001
Waist circumference (cm)	103 ± 10	95 ± 7	<.001

HDL, High-density lipoprotein; *LDL*, low-density lipoprotein; *BMI,* body mass index; *CRP*, C-reactive protein; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure.
Unless otherwise indicated, data are means ± SD, or median and 25th and 75th percentile.

Table III. Treatments in patients with and without metabolic syndrome at the study entry

	Metabolic syndrome		
	Yes (n = 79) (%)	*No (n = 75) (%)*	*P*
Oral hypoglycemic drugs	15 (18.9)	8 (10.6)	.019
Insulin	14 (17.7)	3 (4.0)	<.001
DM patients treated only with hypoglycemic diet	6 (7.6)	3 (4.0)	.141
Statins	58 (73.4)	40 (53.3)	.01
Other hypolipemic drugs	23 (29.1)	5 (6.7)	.001
β-Blockers	27 (34.2)	19 (25.3)	.231
Calcium antagonists	28 (35.4)	34 (45.3)	.211
ACE inhibitors	58 (73.4)	42 (56.0)	.024

DM, diabetes mellitus; *ACE,* angiotensin-converting enzyme inhibitor.

of ABI <0.64 (P = .008). Conversely, the presence of bilateral PAD was not associated with the metabolic syndrome, the prevalence of which was similar in the four groups.

The presence of critical limb ischemia was not associated with a higher prevalence of metabolic syndrome, which was present in six of the 12 critical limb ischemia patients. Only one patient with diabetes and not metabolic syndrome presented critical limb ischemia.

Cardiovascular risk factors and metabolic syndrome. The number of patients with none, one, two, three, four, or five components of the metabolic syndrome was 7 (4.5%), 45 (29.2), 23(14.9), 55 (37.7%), 23 (14.9%), and 1 (0.6%), respectively. Tables II and III summarize, respectively, the characteristics and treatments of the study population according to the presence or absence of the metabolic syndrome.

Hypertension was present in all patients with the syndrome, and hyperglycemia and abdominal obesity were also highly prevalent (79.7% for both). With respect to risk factors not included in the definition of metabolic syndrome, no group difference was observed for age and smoking habit. Conversely, patients with metabolic syndrome had a greater BMI (28.2 [25.6; 29.8] kg/m^2 vs 26.1 [24.8; 27.7] kg/m^2, P < .01), and consequently, a greater prevalence of obesity. Actually, a BMI ≥30

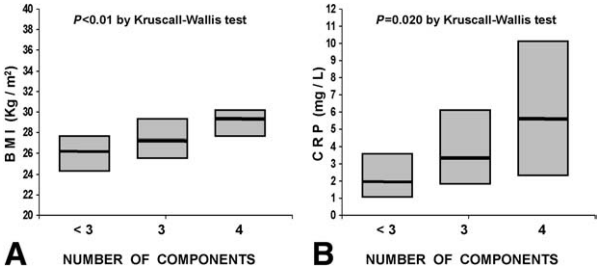

Fig. Body mass index *(BMI)* and serum levels of C-reactive protein *(CRP)* according to the number of components of the metabolic syndrome.

kg/m^2 was present in 22.8% of patients with and in 8.0% of those without the syndrome ($P < .01$). Table I lists BMI values and prevalence of obesity in the groups A, B, C, and D. It is noteworthy that patients with both metabolic syndrome and diabetes had a significantly higher BMI than those with diabetes without metabolic syndrome ($P = .002$).

Metabolic syndrome was associated with a more pronounced inflammatory profile, serum levels of CRP being 3.9 (1.6; 7.6) mg/L in patients with the syndrome and 2.0 (1.1; 3.7) mg/L ($P = .015$) in those without (Table II). Statin use was not associated with reduced levels of CRP in patients with and without metabolic syndrome. Actually, among patients with metabolic syndrome, CRP levels were 3.9 (1.8; 7.3) mg/L in those taking statins and 3.8 (1.8; 7.9) mg/L in those without statin treatment. The corresponding values for patients without metabolic syndrome were 1.7 (1.0; 3.2) mg/L and 2.1 (1.2; 4.8) mg/L. Interestingly, patients with both diabetes and metabolic syndrome had higher CRP levels than those with diabetes and no metabolic syndrome ($P = .023$) (Table I).

Another interesting finding is that both BMI and CRP showed a significant progressive increase with the increase in the number of the components of the metabolic syndrome (Fig). The only patient with all five of the metabolic syndrome components was excluded from this analysis.

Cardiovascular comorbidity and metabolic syndrome. Among PAD patients with metabolic syndrome, a previous myocardial infarction was documented in 46 (58.2%) but was only found in 28 (37.3%) of those without the syndrome ($P < .01$). Table IV shows crude and adjusted odds ratios for the association of previous myocardial infarction with the metabolic syndrome and any of its components. At the univariate analysis, previous myocardial infarction was significantly associated with metabolic syndrome ($P = .008$), low levels of HDL cholesterol ($P = .042$), and high fasting glucose ($P = .036$). After adjustment for age and sex (model I), metabolic syndrome and high fasting glucose maintained a significant association with myocardial infarction ($P = .011$, and $P = .029$, respectively), and low HDL cholesterol approached the statistical significance ($P = .051$). After adjustment for ABI (model II), only the metabolic syndrome was significantly associated with previous myocardial infarction ($P = .034$).

>Table I shows that the differences in the prevalence of previous myocardial infarction between the groups A, B, C, D approached statistical significance ($P = .061$). However, patients with metabolic syndrome and diabetes showed a greater prevalence of previous myocardial infarction than those with diabetes alone ($P = .039$).

No association was found between the metabolic syndrome and previous stroke, three of which had occurred in patients with the syndrome and four in those without. Among the 79 patients with metabolic syndrome, no difference in the prevalence of both myocardial infarction and stroke was found between those with three and those with four components of the syndrome. No significant difference in the prevalence of carotid stenosis >50% and AAA was observed between patients with and without metabolic syndrome (data not shown).

DISCUSSION

Results of the present study confirm the observation that in PAD, metabolic syndrome is highly prevalent[6] and extend the previous findings showing that in these patients, metabolic syndrome is strongly associated with increased levels of CRP, increased BMI, and increased prevalence of previous myocardial infarction.

In the Second Manifestation of Arterial Disease (SMART) study, Gorter et al[6] found that the metabolic syndrome was present in 58% of PAD patients, with women showing a higher prevalence than men (65% vs 55%). These figures are quite similar to those observed in the present study, which also shared with the SMART study the finding that high blood pressure was the component of the metabolic syndrome more often observed in PAD. However, different from that study in which hypertension was followed by low HDL-cholesterol and hypertriglyceridemia, we found that high fasting glucose was the second most prevalent component of the metabolic syndrome in our PAD population. This difference may be important, because insulin resistance is regarded as the primary etiologic process of the metabolic syndrome.[14,15]

We found also that the prevalence of this syndrome was greater in PAD patients with ABI <0.64 (median) than in those with less compromised peripheral circulation. Consistently, in the SMART study,[16] the metabolic syndrome was associated with lower ABI, although this finding was observed not in PAD patients but in subjects with manifest atherosclerotic disease of other vascular beds. In PAD, a reduced ABI is the most powerful negative prognostic indicator, and thus, the observation that it clusters with the metabolic syndrome could imply an even greater risk of future cardiovascular events. We did not find any difference in the prevalence of metabolic syndrome between patients with and without critical limb ischemia; however, this finding may be biased by the low number of 12 patients with critical limb ischemia in our series.

Table IV. Crude and adjusted odds ratios for the association of previous myocardial infarction with the metabolic syndrome and any of its components

	Univariate analysis			*Multivariate analysis*					
				*Model I**			*Model II†*		
	OR	*95% CI*	P	*OR*	*95% CI*	P	*OR*	*95% CI*	P
Metabolic syndrome	2.41	1.26-4.62	.008	2.41	1.23-4.73	.011	2.15	1.06-4.38	.034
High fasting glucose	1.76	1.04-2.99	.036	1.82	1.06-3.13	.029	1.26	0.70-2.27	.442
Hypertension	1.2	0.48-3.01	.7	1.28	0.49-3.29	.612	1.34	0.51-3.55	.555
Hypertriglyceridemia	1.24	0.68-2.23	.484	1.23	0.68-2.22	.499	1.11	0.57-2.16	.752
Low HDL cholesterol	1.99	1.03-3.85	.042	1.99	0.99-3.96	.051	1.78	0.82-3.87	.144
Abdominal obesity	1.05	0.45-2.47	.906	1.13	0.45-2.85	.798	1.22	0.51-2.92	.662

OR, Odds ratio; *CI*, confidence intervals; *HDL*, high-density lipoprotein.
*Model I was adjusted for age and sex.
†Model II was adjusted for ankle/brachial index.

CRP, which negatively correlates with ABI,[17,18] is an independent risk factor for PAD development and severity[19,20] and predicts future cardiovascular events in patients with severe intermittent claudication or critical limb ischemia.[20,21] Furthermore, a recent study[22] reports that elevated CRP levels increase the likelihood of PAD in adults with metabolic syndrome. In the SMART study,[6,16] CRP levels were not assessed, and thus, we believe our data are the first to show a strong association between elevated CRP levels and metabolic syndrome in PAD. We found that the number of components of the metabolic syndrome was significantly associated with increased levels of CRP.

A similar trend in the general population was observed by others[4,23] and probably reflects the fact that elevated CRP levels are associated with many of the components of the metabolic syndrome.[24-26] Three large population studies examined the relationship between CRP, metabolic syndrome, and incident cardiovascular events.[4,27,28] In all three, CRP and metabolic syndrome were both independent predictors of events. Furthermore, in subjects with high CRP levels, the relative risk of events virtually doubled that found with either parameter alone.[4]

At the present, no study has investigated the predictive value of metabolic syndrome in PAD. Future prospective studies will clarify whether the presence of the syndrome in these patients adds to the prognostic value provided by ABI and CRP. BMI, which we found increased in patients with metabolic syndrome, also predicts cardiovascular risk,[29,30] but its prognostic role in PAD is unknown.

A number of studies have shown that the individual risk factors comprising the metabolic syndrome each carry a different odds ratio for predicting prevalent or incident CAD.[4,31,32] In our population of PAD patients, we found that at the univariate analysis, diabetes mellitus, low HDL, and metabolic syndrome were significantly associated with the presence of coexistent CAD, but no relationship was found for hypertriglyceridemia and abdominal obesity. After adjustment for age and sex, only metabolic syndrome and high fasting glucose maintained their predictive value, and low HDL approached statistical significance. However, after adjustment for ABI, which is a powerful marker of systemic atherosclerosis,[33] metabolic syndrome was the only factor to be significantly associated with the presence of CAD.

CONCLUSION

This study first demonstrates that in PAD, metabolic syndrome, which is present in >50% of the affected individuals, is associated with low ABI, high levels of CRP, and increased coexistence of CAD, which are all significant predictors of cardiovascular events in PAD.[11,18,21] Therefore, our data should prompt future prospective studies to assess whether in PAD the presence of metabolic syndrome adds clinically important prognostic information to that provided by ABI and CRP, and whether treating the most important causative factor for the metabolic syndrome (ie, insulin resistance/hyperinsulinemia)[14,15] would be of value in reducing cardiovascular risk. In this regard, it is noteworthy that the newer insulin-sensitizing agents (ie, thiazolidinediones) improve glycemic control, reduce cardiovascular risk factors, and generally result in a beneficial cardiovascular disease profile.[34-36]

AUTHOR CONTRIBUTIONS

Conception and design: GB, MC
Analysis and interpretation: GB, VS, MC
Data collection: VS, GG, EL
Writing the article: GB, GS, MC
Critical revision of the article: GB,VS, GS, GG, EL, MC
Final approval of the article: GB, VS, GS, GG, EL, MC
Statistical analysis: GB, VS, GS
Obtained funding: Not applicable
Overall responsibility: GB

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 2001;285:2486-97.
2. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
3. 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 2002;165:285-92.
4. 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 2003;107:391-7.
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 2002;287:356-9.
6. Gorter PM, Olijhoek JK, van der Graaf Y, Algra A, Rabelink TJ, Visseren FL; SMART Study Group. Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Atherosclerosis 2004;173:363-9.
7. Turhan H, Yasar AS, Basar N, Bicer A, Erbay AR, Yetkin E. High prevalence of metabolic syndrome among young women with premature coronary artery disease. Coron Artery Dis 2005;16:37-40.
8. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam Study. Arterioscler Thromb Vasc Biol. 1998;18:185-92.
9. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317-24.
10. Eberhardt RT, Coffman JD. Cardiovascular morbidity and mortality in peripheral arterial disease. Curr Drug Targets Cardiovasc Haematol Disord 2004;4:209-17.
11. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol 1999;19:538-45.
12. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
13. Leng GC, Lee AJ, Fowkes FGR, Whiteman M, Dunbar J, Housley E, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol 1996;25:1172-81.
14. Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. Diabetologia 1991;34:416-22.
15. Schmidt MI, Watson RL, Duncan BB, Metcalf P, Brancati FL, Sharrett AR, et al. Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central and overall obesity in a general population. Atherosclerosis Risk in Communities Study Investigators. Metabolism 1996;45:699-706.
16. Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL; the SMART Study Group. The metabolic syndrome is associated with advanced vascular damage in patients with coronary artery disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J 2004;25:342-8.
17. Brevetti G, Silvestro A, Di Giacomo S, Bucur R, Di Donato A, Schiano V, et al. Endothelial dysfunction in peripheral arterial disease is related to increase in plasma markers of inflammation and severity of peripheral circulatory impairment but not to classic risk factors and atherosclerotic burden. J Vasc Surg 2003;38:374-9.
18. Vainas T, Stassen FR, de Graaf R, Twiss EL, Herngreen SB, Welten RJ, et al. C-reactive protein in peripheral arterial disease: relation to severity of the disease and to future cardiovascular events. J Vasc Surg 2005;42:243-51.
19. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998;97:425-8.
20. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. Circulation 2005;112:976-83.
21. Rossi E, Biasucci LM, Citterio F, Pelliccioni S, Monaco C, Ginnetti F, et al. Risk of myocardial infarction and angina in patients with severe peripheral vascular disease: predictive role of C-reactive protein. Circulation 2002;105:800-3.
22. Vu JD, Vu JB, Pio JR, Malik S, Franklin SS, Chen RS, et al. Impact of C-reactive protein on the likelihood of peripheral arterial disease in United States adults with the metabolic syndrome, diabetes mellitus, and preexisting cardiovascular disease. Am J Cardiol 2005;96:655-8.
23. Lee WY, Park JS, Noh SY, Rhee EJ, Sung KC, Kim BS, et al. C-reactive protein concentrations are related to insulin resistance and metabolic syndrome as defined by the ATP III report. Int J Cardiol 2004;97:101-6.
24. Schillaci G, Pirro M, Gemelli F, Pasqualini L, Vaudo G, Marchesi S, et al. Increased C-reactive protein concentrations in never-treated hypertension: the role of systolic and pulse pressures. J Hypertens 2003;21:1841-6.
25. Raitakari M, Mansikkaniemi K, Marniemi J, Viikari JS, Raitakari OT. Distribution and determinants of serum high-sensitive C-reactive protein in a population of young adults. The Cardiovascular Risk in Young Finns Study. J Intern Med 2005;258:428-34.
26. Nakanishi N, Shiraishi T, Wada M. Association between C-reactive protein and insulin resistance in a Japanese population: the Minoh Study. Intern Med 2005;44:542-7.
27. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. 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 2003;108:414-9.
28. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380-5.
29. Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. Hypertension 2005;46:654-9.
30. Murphy NF, Macintyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). Eur Heart J 2006;27:96-106.
31. Alexander CM, Landsman PB, Teutsch SM, Haffner SM; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210-4.
32. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP; San Antonio Heart Study. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 2004;110:1251-7.
33. Greenland P, Abrams J, Aurigemma ??, Bond MG, Clark LT, Criqui MH, et al. Prevention Conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. Circulation 2000;101:E16-22.
34. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 2000;23:1605-11.
35. Freed MI, Ratner R, Marcovina SM, Kreider MM, Biswas N, Cohen BR, et al. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. Am J Cardiol 2002;90:947-52.
36. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002;106:679-84.

Submitted Nov 21, 2005; accepted Feb 23, 2006.