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Clinical research

The Metabolic Syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm

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Aims The metabolic syndrome is associated with an increased risk of cardiovascular disease in patients without a cardiovascular history. We investigated whether the metabolic syndrome is related to the extent of vascular damage in patients with various manifestations of vascular disease.

Methods and results The study population of this cross-sectional survey consisted of 502 patients recently diagnosed with coronary heart disease (CHD), 236 with stroke, 218 with peripheral arterial disease (PAD) and 89 with abdominal aortic aneurysm (AAA). Metabolic syndrome was diagnosed according to Adult Treatment Panel III criteria. Carotid Intima Media Thickness (IMT), Ankle Brachial Pressure Index (ABPI) and albuminuria were used as non-invasive markers of vascular damage and adjusted for age and sex if appropriate.

The prevalence of the metabolic syndrome in the study population was 45%. In PAD patients this was 57%; in CHD patients 40%, in stroke patients 43% and in AAA patients 45%. Patients with the metabolic syndrome had an increased mean IMT (0.98 vs 0.92 mm, *P*-value <0.01), more often a decreased ABPI (14% vs 10%, *P*-value 0.06) and increased prevalence of albuminuria (20% vs 15%, *P*-value 0.03) compared to patients without this syndrome. An increase in the number of components of the metabolic syndrome was associated with an increase in mean IMT (*P*-value for trend <0.001), lower ABPI (*P*-value for trend <0.01) and higher prevalence albuminuria (*P*-value for trend <0.01).

Conclusion In patients with manifest vascular disease the presence of the metabolic syndrome is associated with advanced vascular damage.

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Introduction

Several studies showed high prevalences of the metabolic syndrome in different high-risk populations,[1,2] but the magnitude of the metabolic syndrome became apparent when in an apparently healthy population a prevalence of nearly 24% was found.[3] According to Adult Treatment Panel III (ATP III) the metabolic syndrome is diagnosed when three or more metabolic abnormalities (impaired glucose metabolism, elevated blood pressure, hypertriglyceridemia, low HDL cholesterol and central obesity) cluster in the same person.[4] This syndrome confers an increased risk for the development of diabetes mellitus and for cardiovascular morbidity and mortality.[5–8] In a population based cohort study the odds ratio (adjusted for age, sex and follow-up duration) for the development of diabetes in patients with impaired fasting glucose was 10.0 (95% confidence interval 6.1–16.5).[9] The presence of the metabolic syndrome at baseline increased the risk for the development of diabetes mellitus almost 2-fold in American Indians and in Finnish men a roughly 4-fold increase was shown.[10,11] In a study by Lakka et al. men with the metabolic syndrome had a nearly 3-fold increase in cardiovascular related mortality compared to subjects without the metabolic syndrome.[12] In addition, in the Botnia study the risk for coronary heart disease and stroke tripled in metabolic syndrome subjects, with an absolute 10% increase in cardiovascular mortality during 6.9 years of follow-up.[1] This increased cardiovascular risk may be explained by the individual risk factors of the metabolic syndrome in association with other, not routinely measured aspects of the metabolic syndrome as impaired fibrinolysis, oxidative stress, increased small dense LDL, hypercoagulability, inflammation and hyperinsulinaemia.[13]

From several epidemiological studies it became clear that measurement of carotid intima media thickness (IMT) can be applied as a marker for generalized atherosclerosis and as indicator of cardiovascular risk.[14–21] Similarly, microalbuminuria and decreased ankle brachial pressure index (ABPI) are markers of atherosclerosis and indicators of increased cardiovascular risk.[22–26]

It is not yet known, if among patients with already manifest atherosclerotic diseases patients with the metabolic syndrome have an increased risk of future vascular events as compared to patients without this syndrome. Aim of the current cross-sectional study is to evaluate whether patients with manifest vascular diseases and the metabolic syndrome have more vascular damage than their non-metabolic-syndrome counterparts, by means of carotid IMT, ABPI and albuminuria as non-invasive markers for vascular damage.

Methods

Study population

Patients originated from the SMART study (Second Manifestations of ARTerial disease), an on going 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. Study patients were newly referred to the University Medical Centre Utrecht with a manifest atherosclerotic disease (coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm). The delay between diagnosis of the atherosclerotic disease and the time of enrolment varied from 1–40 days. The local Ethics Committee approved the study and all participants gave their written informed consent.

All patients were non-invasively screened for manifestations of atherosclerotic diseases and risk factors other than the qualifying diagnosis. Study design and definitions have been described in detail previously.[27]

Between January 1999 and July 2002 1217 patients with a qualifying diagnosis of coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm entered the study. One hundred and seventy-two patients were excluded from analyses because data were incomplete. So, in the present cross-sectional survey 1045 consecutive patients with clinically manifest atherosclerotic diseases were enrolled: 502 patients recently diagnosed with coronary heart disease (CHD), 236 with stroke, 218 with peripheral arterial disease (PAD) and 89 with an abdominal aortic aneurysm (AAA). Patients with CHD were primarily referred for percutaneous transluminal coronary angioplasty, those with stroke had had a TIA or cerebral infarction, those with PAD were symptomatic and had documented obstruction of distal arteries of the leg and those with AAA had a supra- or infrarenal aneurysm of the aorta (distal aortic anteroposterior diameter $\geqslant$3 cm, measured with ultrasonography).

Study design and methods

At the time of enrolment all patients passed a standardized protocol, including a health questionnaire on current medication use, past medical history, familial vascular history and atherosclerotic risk factors. Length, body weight, waist circumference and blood pressure were measured. Fasting blood was sampled to determine lipid, serum glucose, homocysteine and creatinine levels, and a morning urine portion was collected for measuring albumin and creatinine concentrations. Creatinine was measured with a commercial enzymatic dry chemistry kit (Johnson and Johnson) and albumin was determined with an immunoturbidimetric assay (Boehringer-Mannheim). Intima media thickness (IMT) was measured in supine position in the left and right common carotid arteries in anterolateral, posterolateral and mediolateral direction, the head turned 45 degrees away from the side being scanned. An ATL Ultramark 9 (Advanced Technology Laboratories, Bethel, WA, USA) equipped with a 10 MHz linear array transducer was used. Reference point for measurement of the IMT was the onset of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. An R-wave-triggered optimal longitudinal image of the far wall was frozen and stored on video-tape. On this image, the leading edges corresponding to the transition zone between lumen-intima and media-adventitia were traced, over a length of 1 cm proximal to the reference point and the total intima-media surface of this selected area was calculated.[27] The mean IMT of these six measurements was calculated only, if at least four of six measurements were available.

The resting ankle-brachial pressure index (ABPI) was measured with the subject in supine position with an 8-Mhz continuous-wave Doppler probe connected to an IMEXLAB 9000 Vascular Diagnostic System (Imex Medical Systems Inc., Golden, CO, USA). Blood pressure was taken from both arms using a semiautomatic oscillometric device (Omega 1400, Invivo Research Laboratories Inc.). The value of the highest systolic

blood pressure measured at the ankle was divided to the highest blood pressure measured in both arms. The ratio (ABPI) was calculated for both legs.

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 high-density lipoprotein (HDL) cholestrol (serum HDL-cholesterol <1.04 mmol/l (40 mg/dl) in men and <1.29 mmol/l (50 mg/dl) in women), high fasting glucose (fasting serum glucose ≥6.1 mmol/l (110 mg/dl)).[4]

Patients on glucose-lowering agents or anti-hypertensive medication were regarded as having high fasting glucose and high blood pressure, respectively.

A fasting glucose ≥7.0 mmol/l in patients with no history of diabetes mellitus was considered as newly diagnosed diabetes mellitus. Established diabetes was defined as self-reported diabetes.

Albuminuria was calculated as the ratio of albumin to creatinine (mg albumin/mmol creatinine). Albuminuria is defined as a ratio >3 mg albumin/mmol creatinine.[28,29]

A decreased ABPI was defined as ABPI in rest $\leqslant$0.90 in at least one leg.[30–32]

Outcomes of interest

Outcomes of interest were mean IMT, percentage patients with a decreased ABPI and percentage patients with albuminuria in patients with and without the metabolic syndrome. Patients were categorized in subpopulations of cardiovascular disease.

Statistical analyses

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

To adjust mean IMT for age and sex differences between patients with and without the metabolic syndrome we used analysis of covariance (ANCOVA, general linear model procedure).

We adjusted the percentage of patients with decreased ABPI and albuminuria for age and sex differences between patients with and without the metabolic syndrome.

With linear regression analysis the influence of age and sex on ABPI and albuminuria was investigated. Subsequently, in case of a significant influence, means of ABPI and albuminuria were calculated and adjusted values were calculated by adding mean value and residual for each patient. Subsequently cut off values as defined earlier (ABPI $\leqslant$0.90 and albuminuria as a ratio >3 mg albumin/mmol creatinine) were applied.

Trends between the number of components of the metabolic syndrome and IMT was investigated with linear regression analysis, between number of components and ABPI and albuminuria with logistic regression analysis. If appropriate these outcomes were adjusted for age and sex.

When ABPI was the outcome of interest, patients with peripheral arterial disease were excluded from analyses.

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 10.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

In Table 1 the baseline characteristics of the study population are listed, according to the presence of the metabolic syndrome: 469 patients (45%) with the metabolic syndrome, and 576 patients without (55%). Age and smoking habits were equally distributed. Patients with the metabolic syndrome had a higher creatinine clearance compared to non-metabolic syndrome patients (79 ml/min vs 76 ml/min, *P*-value 0.01). As expected, all five diagnostic parameters of the metabolic syndrome were more prevalent in patients with the metabolic syndrome than in patients without the metabolic syndrome (*P*-value <0.001). Besides this, 21% of the patients with the metabolic syndrome had a history of a vascular disease in another vascular bed compared to 16% in the non-metabolic syndrome population (*P*-value 0.02). From 469 patients diagnosed with the metabolic syndrome, 179 (38%) had a normal fasting glucose level and did not use glucose lowering agents.

Outcomes of interest

Age and sex significantly influenced the relationship between the metabolic syndrome and IMT and ABPI. The relationship between albuminuria and metabolic syndrome was influenced by age not by sex.

Patients with the metabolic syndrome had an increased mean IMT (0.98 mm vs 0.92 mm, *P*-value <0.01) and an increased prevalence of albuminuria (20% vs 15%, *P*-value 0.03) compared to non-metabolic syndrome patients. A trend, albeit non significant, toward a decreased ABPI in patients with the metabolic syndrome was found (*P*-value 0.06) (Table 2).

Similar relationships were found in all subpopulations of (cardio)vascular disease, except for IMT in AAA patients (1.04 mm vs 1.09 mm).

The prevalence of albuminuria was 28% in diabetic patients. After exclusion of patients on glucose-lowering agents, patients with the metabolic syndrome still had higher prevalences of albuminuria than patients without (16% vs 12%). Similar observations were made when patients with anti-hypertensive drugs were excluded from analyses (18% vs 10%).

In Table 3 it is shown that the number of single components of the metabolic syndrome is associated with an increase in mean IMT, in the prevalence of albuminuria and in the proportion of patients with decreased ABPI. Patients who had all five criteria constituting the metabolic syndrome had the largest IMT (1.07 mm), the highest frequency of a decreased ABPI (22%), and the highest prevalence of albuminuria (24%) compared to patients with less than five components.

Table 1 Baseline characteristics of the study population

	Metabolic Syndrome No (*n*=576)	Yes (*n*=469)	*P*-value
Male gender	84	74	<0.001
Age (years)	59±10	60±10	0.4
Body mass index (kg/m^2)[1]	25±3	28±4	<0.001
Smoking[a]	82	81	0.8
History of other vascular disease[b]	16	21	0.02
Total Cholesterol (mmol/l)[2]	5.2 (4.5–5.9)	5.6 (4.8–6.2)	<0.001
Homocysteine (μmol/l)[1]	14±6	15±7	0.2
Serum creatinine (μmol/l)[1]	93±37	95±46	0.4
Creatinine clearance (Cockcroft) ml/min[1]	76±19	79±22	0.01
Diabetes mellitus[c]	7	33	<0.001
Glucose lowering agents	4	18	<0.001
Anti-hypertensive drugs	25	45	<0.001
Lipid lowering agents	38	38	0.4
Components of metabolic syndrome			
Waist circumference (cm)[1]	92±9	10±10	<0.001
Blood pressure systolic (mmHg)[1]	134±21	143±20	<0.001
Blood pressure diastolic (mmHg)[1]	78±11	81±10	<0.001
HDL-Cholesterol (mmol/l)[2]	1.21 (1.04–1.42)	0.96 (0.83–1.11)	<0.001
Triglycerides (mmol/l)[2]	1.33 (1.05–1.65)	2.12 (1.72–2.78)	<0.001
Fasting serum glucose (mmol/l)[2]	5.6 (5.2–5.9)	6.2 (5.6–7.2)	<0.001

All data in percentages, or as indicated: [1]mean±standard deviation or [2]median with interquartiles range.
HDL: high-density lipoprotein.

[a]Still smoking, recently stopped smoking or previously smoking.
[b]History of vascular disease other than qualifying diagnosis.
[c]Fasting serum glucose $\geqslant$7.0 mmol/l or self-reported diabetes.

Table 2 Non-invasive atherosclerotic markers for vascular damage in all patients and in subpopulations of cardiovascular disease in relation to the presence of the metabolic syndrome

	Metabolic Syndrome	Patients %(n)	IMT (mm) Mean±se	*P*-value	decreased ABPI[a] %	*P*-value	Albuminuria %	*P*-value
All patients	No	55 (576)	0.92±0.01		10		15	
	Yes	45 (469)	0.98±0.01	<0.01	14	0.06	20	0.03
CHD	No	29 (299)	0.85±0.01		5		13	
	Yes	19 (203)	0.89±0.02	0.04	7	0.3	13	0.9
Stroke	No	13 (135)	1.00±0.03		18		15	
	Yes	10 (101)	1.06±0.03	0.2	24	0.3	27	0.02
PAD	No	9 (93)	0.90±0.04		–		18	
	Yes	12 (125)	1.02±0.03	0.02	–		24	0.3
AAA	No	5 (49)	1.09±0.07		20		16	
	Yes	4 (40)	1.04±0.08	0.7	28	0.4	23	0.5

se: standard error.
CHD: coronary heart disease.
PAD: peripheral arterial disease.
AAA: abdominal aortic aneurysm.
IMT: Intima Media Thickness in common carotid arteries (age- and sex adjusted).
Decreased ABPI: Ankle Brachial Pressure Index $\leqslant$0.90 in at least one leg (age- and sex adjusted).
Albuminuria: albumin/creatinine ratio >3 mg/mmol (urine portion) (age-adjusted).

[a]Patients with PAD excluded from analyses.

Discussion

This study detected a high prevalence of the metabolic syndrome in patients with manifest atherosclerotic arterial disease. Moreover, the presence of the metabolic syndrome was associated with more advanced atherosclerosis, measured by non-invasive techniques. Patients with the metabolic syndrome had an increased carotid IMT, more often a decreased ABPI and had a higher prevalence of albuminuria compared to patients without

Table 3 Components of the metabolic syndrome in relation to IMT, decreased ABPI and the prevalence of albuminuria

Metabolic syndrome components (*n*)	IMT (mm) mean±se	*P*-value[b]	Decreased ABPI[a] (%)	*P*-value[b]	Albuminuria (%)	*P*-value[b]
0	0.85±0.04		2		13	
1	0.90±0.02		10		13	
2	0.94±0.02		12		16	
3	0.95±0.02		11		18	
4	0.97±0.03		18		21	
5	1.07±0.04	<0.001	22	<0.01	24	<0.01

IMT: Intima Media Thickness in common carotid arteries (age- and sex adjusted).
Decreased ABPI: Ankle Brachial Pressure Index ≤0.90 in at least one leg (age- and sex adjusted).
Albuminuria: albumin/creatine ratio >3 mg/mmol (urine portion) (age-adjusted).
se: standard error.

[a] Patients with PAD excluded from analyses.
[b] *P*-value for trend.

the metabolic syndrome. In addition, an increment in the number of components constituting the metabolic syndrome was associated with an increase in mean IMT, lower ABPI values and higher prevalence of albuminuria.

In patients with a negative history of vascular disease, IMT, ABPI and albuminuria are markers for atherosclerosis, associated with an increased risk for cardiovascular morbidity and mortality. Several studies found that these non-invasive markers could also be applied to patients with manifest vascular disease. Previously we showed that common carotid IMT appeared to be a clear marker of cardiovascular risk in patients with either manifest vascular disease or atherosclerotic risk factors.[33] Assessment of microalbuminuria in the first week after a myocardial infarction was a strong predictor for 1-year mortality.[34] In the PREVEND study the presence of microalbuminuria in patients with ST-T segment abnormalities on a resting ECG conferred an increased (cardiovascular) mortality risk.[35] In patients with peripheral arterial disease or suspected coronary artery disease the ABPI was a predictor of cardiovascular events.[36–38] Our study demonstrates that these well-established indicators of increased cardiovascular risk cluster with the metabolic syndrome. This implies that identification of the metabolic syndrome in this high-risk category of patients could indicate an even greater risk of cardiovascular events.

C-reactive protein (CRP) is regarded as a sensitive indicator of cardiovascular risk, and could also be directly involved in atherogenesis.[39] Unfortunately in this study we were not able to assess CRP levels. In apparently healthy women plasma CRP concentration increases with the number of individual components of the metabolic syndrome.[7] Moreover, a significant linear relationship between CRP levels and plasma insulin concentrations was observed,[40] suggesting that in metabolic syndrome patients without cardiovascular history CRP could be used as indicator of the increased associated cardiovascular risk.

The presence of the metabolic syndrome in nearly 50% of subjects referred for treatment of an atherosclerotic arterial disorder (subjects with overt diabetes mellitus excluded) calls for a systematic approach to identification and treatment of this syndrome. The individual components that make up the syndrome should be treated coherently, with awareness of the underlying disorder: insulin resistance. Newly developed drugs such as the peroxisome proliferator-activated receptor (PPAR) agonists may help to reach targets, along with life style modifications.[41,42]

Remarkably, in our study nearly 40% of the patients diagnosed with the metabolic syndrome had normal fasting glucose and did not use glucose lowering agents. As insulin resistance is regarded as one of the major pathophysiological disturbances underlying the metabolic syndrome, normal glucose levels in these patients are most likely the result of a compensatory hyperinsulinaemic state, associated with increased cardiovascular risk.[43] Although insulin has beneficial effects on endothelial function by enhancing eNOS transcription, hyperinsulinaemia is associated with endothelial dysfunction by stimulating the release of the potent vasoconstrictor endothelin.[44] Since normal glucose values do not exclude insulin resistance, also in euglycemic vascular patients the metabolic syndrome should be considered.

We acknowledge some limitations of our study. Firstly, the metabolic syndrome can be diagnosed by several definitions, which implies that it may be difficult to compare outcomes of different studies. Most commonly used are the definitions proposed by The World Health Organization in 1998, and the working definition suggested by Adult Treatment Panel III.[4,45] Ford et al. compared the prevalence of the metabolic syndrome in a non-institutionalised population in the United States with the above mentioned definitions.[46] For the entire population, no difference in prevalence was found but differences in subpopulations were masked, particularly in race or ethnic groups. Because of this agreement, and also because the components according to ATP III are more easy to measure in daily clinical practice we decided to use this definition of the metabolic syndrome.

Secondly, this survey is a cross sectional study, so only assumptions about possible aetiological relationships can be made.

We conclude that in patients with already manifest vascular diseases, the metabolic syndrome is associated with more advanced vascular damage as measured by indicators for increased (cardio)vascular risk. Screening in a high-risk population for the metabolic syndrome identifies patients at higher cardiovascular risk which may guide pharmacological and non-pharmacological therapies in order to prevent new cardiovascular incidents.

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