Frequency and characteristics of metabolic syndrome in patients with symptomatic carotid atherosclerosis

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Background: *Metabolic syndrome (MetS) is associated with increased risk of carotid atherosclerosis.* ***Aim:*** *To estimate the frequency of MetS in patients with symptomatic carotid atherosclerotic disease, and to compare clinical, biochemical and ultrasonographic characteristics of patients with and without MetS.* ***Material and methods:*** *Cross-sectional study of 657 consecutive patients (412 males) with symptomatic carotid atherosclerotic disease. Carotid atherosclerosis was estimated by high resolution B-mode ultrasonography. National Cholesterol Education Program (NCEP) III criteria were used for estimation of MetS.* ***Results:*** *Metabolic syndrome was present in 55.6% of studied patients. Among patients with metabolic syndrome there was a significantly higher proportion of women, and mean values of body weight, body mass index, waist circumference, percentage of body fat, systolic and diastolic blood pressure, serum triglycerides, total cholesterol and glucose were significantly higher. Mean values of high density lipoprotein cholesterol and alcohol consumption were significantly lower in patients with MetS. No differences between patients with or without MetS, were observed for age, smoking, mean values of low density lipoprotein cholesterol, high sensitive C-reactive protein and fibrinogen, and for degree of carotid stenosis or severity of clinical manifestations.* ***Conclusion:*** *Half of these patients with carotid stenosis have features of the metabolic syndrome (Rev Méd Chile 2009; 137: 329-36).*

(***Key words:*** *Carotid artery diseases; High density lipoprotein cholesterol; Metabolic syndrome)*

Frecuencia y características del síndrome metabólico en pacientes con estenosis carotídea sintomática

Antecedentes: *El síndrome metabólico se asocia a un mayor riesgo de ateroesclerosis carotídea.* ***Objetivo:*** *Evaluar la frecuencia de síndrome metabólico en pacientes con ateroesclerosis carotídea sintomática y comparar las características clínicas, bioquímicas y ultrasonográficas en pacientes con y sin síndrome metabólico.* ***Material y método:*** *Estudio transversal de 657 pacientes consecutivos (412 varones) con ateroesclerosis carotídea sintomática. El síndrome metabólico fue diagnosticado de acuerdo a los criterios del National Cholesterol Education Program (NCEP) III. La ateroesclerosis carotídea se investigó mediante ultrasonografía de alta resolución modo B.* ***Resultados:*** *Se diagnosticó síndrome metabólico en 55.6% de los pacientes estudiados. Entre los sujetos portadores del síndrome había una mayor proporción de mujeres y el peso, índice de masa corporal, circunferencia de cintura, porcentaje de grasa corporal, presión arterial sistólica y diastólica y niveles séricos de triglicéridos, colesterol total y glicemia fueron mayores. Los valores promedio de colesterol HDL y de consumo de alcohol fueron significativamente menores en los pacientes con síndrome metabólico. Los pacientes con el síndrome consumían menos alcohol y tenían niveles de colesterol HDL más bajos. No se encontraron diferencias entre sujetos con y sin síndrome metabólico en edad, tabaquismo, lipoproteínas de baja densidad, proteína C reactiva ultrasensible, fibrinógeno, grado de estenosis carotídea o severidad de sus manifestaciones clínicas.* ***Conclusiones:*** *La mitad de estos pacientes con estenosis carotídea tiene un síndrome metabólico.*

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Metabolic syndrome (MetS) has become one of the major public-health challenges worldwide[1]. From the end of the seventh decade and the beginning of the eighth decade in the 20th century, clustering of cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia and obesity, and their association with atherosclerosis was recognized[2]. In 1988 Reaven was first to describe Syndrome X, and defined it as a cluster of hypertension, glucose intolerance, elevated tryglycerides and low level of high density lipoprotein (HDL) cholesterol[3]. In 1991 Ferrannini et al suggested that this clustering was caused by insulin resistance and called it insulin resistance syndrome[4]. In 1999, WHO defined the syndrome and changed its name to metabolic syndrome[5]. In 2001 the National Cholesterol Education Program - Adult treatment Panel III (NCEP-ATP III) proposed both diagnostic criteria for metabolic syndrome and cut-off points for its components[6].

There is increasing evidence that metabolic syndrome can influence the progression of atherosclerosis and that subjects with metabolic syndrome have increased risk of atherosclerotic disease (coronary heart disease and stroke) morbidity and mortality[7]. General atherosclerosis has been found to be related to carotid atherosclerosis, which can be successfully detected by the use of B-mode ultrasonography. There are abundant data about the independent association between the individual components of MetS and vascular structure and function[8,9], which in turn have also been recognized as independent predictors of adverse cardiovascular events[10].

The aim of the present study was to estimate the frequency of MetS in patients with carotid atherosclerosis and to compare clinical, biochemical and ultrasonographic characteristics of patients with and without MetS.

Material and methods

This cross-sectional study involved 657 consecutive patients with verified carotid atherosclerotic disease who referred to the Vascular Surgery Clinic Dedinje in Belgrade during the period April 2006 - November 2007. In the study were included subjects who had symptoms of cerebral ischemia (amaurosis fugax, transient ischemic attack, stroke), and carotid stenosis of ≥50%, according to NASCET criteria[11]. Carotid atherosclerosis was estimated by high resolution B-mode ultrasonography HDI, ATL 3500. Patients under eighteen years of age and patients with malignant disease, previous endarterectomy or rheumatoid arthritis were excluded.

For all participants anthropometric parameters and data on cardiovascular risk factors were collected.

Anthropometric parameters. Body weight was assessed by using a calibrated standard balance-beam, height was measured by a standard height bar, and Body Mass Index (BMI) was calculated as weight (kg) divided by height (m^2) and categorized according to WHO criteria[12]. Waist circumference was measured at the midway between lower rib and crista iliaca, and according to WHO criteria all patients were classified into two groups: patients with abdominal obesity, defined by a waist circumference (WC) >102 cm (men) and >88 cm (women), and patients without it[12]. Body fat was calculated according to method proposed by Durnin and Womersley[13].

Blood pressure. Blood pressure measurements were done by using appropriately sized cuffs and auscultatory method recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[14].

Biochemical tests. For estimation of metabolic parameters, fasting blood glucose (FBG) and lipoproteins, blood samples were obtained after an overnight fast and avoidance of liquids. Levels of FBG, total cholesterol (TC), serum triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were estimated using commercial kits (Abbot, IL,USA) on an automated analyzer (AEROSET™, Abbot, IL, USA). Levels of high sensitivity C-reactive protein (hsCRP) and fibrinogen (reference values 2-4g/L) were measured by using Immunoturbidimetric fixed time test (Olympus Diagnostics, O'Callaghan's Mills Co. Clare, Ireland).

Metabolic syndrome. According to NCEP III criteria MetS is present when 3 or more of the

following determinants are met: (1) fasting blood glucose level ≥6.11 mmol/L (2) plasma triglycerides ≥1.69 mmol/L; (3) plasma HDL-C <1.03 mmol/L in men and <1.29 mmol/L in women; (4) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or antihypertensive drug therapy; and (5) waist circumference >102 cm in men and >88 cm in women[6].

Smoking and alcohol consumption. Data about smoking and alcohol consumption were collected by the use of the questionnaire. Each subject was classified as a non-smoker, former smoker, or current smoker, but for the purpose of the present study "ever smoker" status (current or former) was used. The same classification was used for alcohol consumption. Alcohol consumption was analyzed in 2 ways, as a) alcohol consumption yes/no variable and b) by calculating the total dose of alcohol consumption for each participant by adding all the individual beverages weighted to their alcohol content. It was assumed that alcohol content in the beverages was as follows: 30% in brandy, 40% in hard liquor, 12% in wine, and 3.5% in beer.

Statistical analysis. Continuous variables were described as means ± standard deviation (SD), and categorical variables were presented by counts and percentages. In analysis of data chi square test and two-tailed t-test were used. Normality of data distribution was assessed by Kolmogorov- Smirnov test. For parameters with asymmetric distribution of results, t-test was performed after their logarithmic transformation. Significance level was set at $p < 0.05$. Data were analyzed using SPSS package version 9.

Ethics. The study was reviewed and given ethical approval by the Ethics Committees at the School of Medicine in Belgrade. All patients gave written, informed consent.

Results

Study group comprised 412 men and 245 women. Out of 657 patients, metabolic syndrome was present in 55.6% (in 49.8% of men and 65.3% of women).

In MetS positive patients each of MetS components was frequently present (in above 70.0% of patients) with the exception of increased fasting glucose which was found in 37.3% of them (Table 1). Increased waist circumference, elevated blood pressure and hypertriglyceridaemia were the most commonly combined abnormalities. In MetS negative patients, the frequency of all MetS components was significantly lower, the combined increase of waist circumference and triglycerides being the least frequently found.

Table 1. Metabolic syndrome constituents and their distribution in patients with and without metabolic syndrome

Variable	MetS - (n =292)	MetS + (n =365)	P-value
Increased waist circumference[a]	18.8%	73.7%	<0.001
Increased triglycerides[b]	13.4%	73.4%	<0.001
Low HDL - cholesterol[c]	38.0%	81.6%	<0.001
Increased fasting glucose[d]	8.6%	37.3%	<0.001
Increased blood pressure[e]	78.8%	96.4%	<0.001
Increased waist circumference and triglycerides[a,b]	1.03%	51.5%	<0.001
Number of constituents (mean ± SD)	1.54 ± 0.57	3.62 ± 0.67	<0.001

MetS: metabolic syndrome; HDL: high-density lipoprotein; SD: standard deviation
[a]>102 cm in men and >88 cm in women. [b]≥1.69 mmol/L. [c]<1.03 mmol/L in men and <1.29 mmol/L in women. [d]≥6.11 mmol/L. [e]≥130/≥85 mm Hg or on antihypertensive drug treatment in a patient with a history of hypertension.

Out of patients without MetS, eleven subjects (nine men and two women) had none of its constituents (Table 2). Among those with MetS, about half had four or even all five MetS constituents.

Compared with MetS negative patients, patients with metabolic syndrome were significantly more frequently women and had significantly higher mean values of body weight, body mass index, waist circumference, as well as higher percent of body fat. Alcohol consumption was significantly less frequent in MetS positive patients. MetS positive and MetS negative patients did not differ in their age, and smoking habit (Table 3).

Table 2. Prevalence of the number of metabolic syndrome constituents in the study patients

	Number of metabolic syndrome components					
Gender	0	1	2	3	4	5
Male (n =412)	9	81	117	107	82	16
	(2.2%)	(19.7%)	(28.4%)	(26.0%)	(19.9%)	(3.9%)
Female (n =245)	2	30	53	71	66	23
	(0.8%)	(12.2%)	(21.6%)	(29.0%)	(26.9%)	(9.4%)
Total (n =657)	11	111	170	178	148	39
	(1.7%)	(16.9%)	(25.9%)	(27.1%)	(22.5%)	(5.9%)

Table 3. Some anthropometric and demographic characteristics and habits of patients with and without metabolic syndrome

Variable	MetS - (n =292) Mean ± SD/ %	MetS + (n =365) Mean ± SD/ %	P-value
Age (years)	65.44 ± 9.20	65.19 ± 7.65	0.406
Body weight (kg)	71.16 ± 11.94	79.50 ± 13.16	<0.001
Body height (cm)	167.94 ± 8.81	166.36 ± 9.18	0.026
BMI (kg/m^2)	25.13 ± 3.26	28.65 ± 3.89	<0.001
WC (cm)			
Men	94.86 ± 8.95	103.89 ± 9.65	<0.001
Women	84.60 ± 9.29	98.25 ± 9.66	
Percent of body fat			
Men	25.94 ± 4.89	29.78 ± 4.46	<0.001
Women	35.42 ± 4.55	39.33 ± 4.27	
Women	29.1%	43.8%	<0.001
Ever smokers	67.8%	64.1%	0.321
Alcohol consumption	41.4%	33.2%	0.029
Daily alcohol consumption, dL:			
mean ± SD	0.22 (0.53)	0.20 (0.50)	0.128
median and range	0 (0.00 – 7.00)	0 (0.00 – 5.25)	
IQR	0.35	0.35	

MetS: metabolic syndrome; SD: standard deviation; BMI: body mass index; WC: waist circumference; IQR: interquartile range

Some clinical and biochemical characteristics of patients with and without MetS are presented in Table 4. Patients with MetS had significantly higher both systolic and diastolic blood pressure. Of biochemical characteristics, mean values of triglycerides, total cholesterol and glucose were significantly higher in MetS positive patients, whereas a mean value of HDL-cholesterol was significantly lower. Compared groups did not differ in values of LDL-cholesterol, hs C-reactive protein and fibrinogen (Table 4).

Patients with and without metabolic syndrome did not differ significantly either in the grade of carotid stenosis or in the grade of its clinical manifestation (Table 5). The results did not change after adjustment on possible confounding factors (sex, total cholesterol, alcohol consumption, percent of body weight and BMI).

Table 4. Clinical and biochemical characteristics of patients with and without metabolic syndrome

Variable	MetS - (n = 292) Mean ± SD/%	MetS + (n = 365) Mean ± SD/%	P-value
SBP (mm Hg)	140.02 ± 20.70	144.96 ± 18.90	<0.001
DBP (mm Hg)	81.03 ± 11.12	84.12 ± 9.55	<0.001
TG (mmol/L)	1.35 ± 0.52	2.26 ± 1.07	<0.001
TC (mmol/L)	5.11 ± 1.22	5.34 ± 1.32	0.025
HDL– cholesterol (mmol/L)			
Men	1.11 ± 0.33	0.92 ± 0.19	<0.001
Women	1.29 ± 0.30	1.05 ± 0.22	
FBG (mmol/L)	4.91 ± 1.06	5.85 ± 1.95	<0.001
LDL – cholesterol (mmol/L)	3.33 ± 1.31	3.41 ± 1.14	0.359
hsCRP (mg/L)	4.08 ± 6.36	3.94 ± 6.21	0.471
Fibrinogen (g/L)	3.40 ± 1.10	3.35 ± 1.01	0.567
History of antihypertensive therapy	42.7%	57.3%	0.008
History of antilipids therapy	38.3%	61.7%	0.009

MetS: metabolic syndrome; SBP: systolic blood pressure; DBP: diastolic blood pressure TG: triglycerides; TC: total cholesterol; HDL: high-density lipoprotein; FBG: fasting blood glucose; LDL: low-density lipoprotein; hsCRP: high sensitive C-reactive protein

Table 5. Carotid stenosis and clinical manifestations of carotid atherosclerotic disease in patients with and without metabolic syndrome

Variable	MetS - (n =292)	MetS + (n =365)	P-value
Carotid stenosis ≥70%	85.9%	82.6%	0.279
Clinical manifestation of carotid disease:			
Amaurosis fugax	32.9%	35.9%	0.124
Transient ischemic attack	27.4%	24.7%	0.426
Stroke	39.7%	39.4%	0.943

MetS - metabolic syndrome

Discussion

In the present study, in which NCEP criteria were used, 55.6% of patients with carotid atherosclerosis had MetS, and MetS prevalence was higher in women than in men (65.3% vs. 49.8%). Hypertension, abdominal obesity and hypertrigliceridemia were the most frequently combination of metabolic abnormalities.

Metabolic syndrome is highly prevalent in the developed countries. According to the NCEP criteria, the age adjusted prevalence of the MetS in the US population was estimated at 23.7%, and increased to 43.5% in adults who were older than 60 years[6]. MetS prevalence is higher in population with verified atherosclerotic disease. According to Gorter et al. study, the prevalence of MetS in various types of atherosclerotic disease was in range from 41% in patients with coronary heart disease, up to 58% in patients with peripheral arterial disease[15]. In the same study the prevalence of MetS in cerebrovascular diseases was 43%. Trevisan et al, also found that among patients older than 50 years, MetS prevalence was higher in women than in men[16]. In the general population of USA there was no difference according to gender before 70 years of age, but among older subjects, women had a higher prevalence[17]. According to the results of Iglseder et al. study[18] and Kawamoto R et al study[19], the effect of MetS on early atherosclerosis (assessed by number and diameter of plaques – B-score and/ or intima media thickness - IMT) is more pronounced in women than in men, and the impact of MetS components on IMT differs between men and women. The authors postulated that a partial explanation of gender-related difference may involve the influence of sex hormones. Support for the genetic mechanisms of sex differences is provided by animal models[20] and investigations involving male and female twins[21]. Obesity, and particularly visceral (abdominal, central) obesity, has been considered as a significant predictor of atherosclerotic disease. According to many studies, WC and percent of body fat are more important than BMI in predicting cardiovascular events and their consequences[22], and obesity expressed by WC was recommended as the most important risk factor for cardiovascular events[6]. Visceral obesity has been related to dislipidemia (increased levels of triglycerides and very-low-density lipoproteins, and low level of HDL - cholesterol) and insulin resistance[23]. It is now recognized that adipose tissue is not only depo of fat, but an endocrine organ which is probably an important link between increased fat mass and insulin resistance. It also produces several inflammatory products that affect atherosclerotic process[24]. Many epidemiological studies have shown that inflammation is associated with the process of atherosclerotic disease. CRP, especially estimated crosswise hsCRP is connected with various type of atherosclerosis[25]. Also, Takahashi et al, found that the level of CRP was significantly correlated with the increased number of risk factors[26]. But, the mechanism of this process is still unclear. Beside hsCRP, a few other mediators can predict a cardiovascular events (serum amyloid A, IL-6, homocysteine), but the high hsCRP concentration had a stronger relationship with stroke[27]. In the present study mean values of body weight, BMI, WC and percent of body fat were significantly greater in patients with MetS, increased WC being about four times more frequent in MetS positive patients in comparison with MetS negative patients. Hypertension has been recognized as a strong risk factor for atherosclerotic disease[28]. In SU.VI.MAX Vascular study, elevated blood pressure was found to be the most important MetS component in relation to structure and function of large arteries[29]. Hypertension, hypertriglyceridaemia and low HDL-cholesterol were the most common combination of abnormalities in cross sectional study which included 1117 patients with atherosclerotic disease[15]. In the present study increased blood pressure was the predominant MetS constituent in all patients, significantly more frequently present in MetS positive subjects. Elevated blood pressure, hypertriglyceridaemia and high waist circumference were the most common combination of MetS components. There was no significant association between MetS and either hsCRP or fibrinogen. We also did not find relationship between smoking and MetS, although some prospective studies suggested this association[30]. Data about relationship of alcohol consumption and carotid atherosclerosis are controversial. The positive association was observed in some studies[31], but on the other hand moderate alcohol consumption was found to have protective effect

on carotid atherosclerosis[32]. There are several studies showing that subjects with MetS had a significantly greater extent of carotid atherosclerosis expressed as intima media thickness[33], arterial stiffness[34], or carotid plaques occurrence[35]. On the other hand, in some studies MetS was not significantly related to the presence of carotid plaques, and blood pressure was the only MetS component associated with all vascular parameters[25]. The authors hypothesized that the predominant effect of BP on vascular parameters could be in part explained by the fact that increased BP was the most frequent abnormality in their study population[25]. They also questioned the possibility that use of other, higher cut-off for BP instead of that proposed by NCEP would modify the prevalence of the abnormalities among studies.

More than a half of the patients in the present study had MetS, but neither carotid stenosis nor its clinical manifestations were related to it. Increased blood pressure was the most frequent abnormality in our study population but it also was not more frequent in subjects with higher grade of carotid stenosis. The same was true for other MetS components (higher level of tryglicerides was even more frequent in those with carotid stenosis <70%). These findings could be most probably explained by the study design. The study is cross-sectional and study population comprised patients and in majority of them carotid stenosis was ≥70%. It remains unknown how long these patients were exposed to risk factors for atherosclerosis. All participants had clinical manifestation of carotid atherosclerosis and there is possibility that analyzed variables might be changed after the events. It is also evident that atherosclerosis can develop in subjects with two or only one of MetS components, even in those without any of them which points out to the importance of some other risk factors like genetic one.

The results of the present study underline the need to prevent and control each one of the MetS components in early period of life as recommended by the ATP III guidelines.

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