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ASSOCIATION OF THE NUMBER OF COMPONENTS OF THE MEATBOLIC SYNDROME AND CAROTID ARTERY DISEASE

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Abstract

Metabolic syndrome (MetS) is a group of at least three of the following metabolic disorders: central obesity, elevated glycaemia, high serum triglycerides, low serum high-density lipoprotein (HDL), and high blood pressure. Carotid artery disease (CAD) involves changes in the arterial wall that cause thickening of the intima-media (IMT), narrowing, or complete obstruction of the carotid artery lumen. Objective:To determine the impact of the number of MetS components on CAD.

This analytical unicenteric cross-sectional study included 80 subjects with MetS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. CAD was diagnosed with the Esaote My Lab70 HVG device, with a linear probe (7.5 MHz), according to the Ultrasound consensus criteria for CAD of the Association of Radiologists (2002, San Francisco).

34 subjects (42.5%) had 4 components of MetS, 24 subjects (30%) had 3 components, 22 subjects (27.5%) had 5 components. Gender and age have no statistically significant effect on the influence of metabolic risk factor as components of MetS ($p = 0.38$, $p = 0.72$, respectively). CAD was diagnosed in 77 subjects (96.25%), in 21 subject (87.5%) with 3 components of MetS and in all subjects with 4 and 5 components of MetS.

This statistically confirmed that subjects with a smaller number of MetS components significantly have less CAD ($p = 0.026$). The increase in the number of components and the synergistic effect of individual MetS components is significantly associated with CAD.

Keywords: metabolic syndrome, carotid artery disease

Introduction

Metabolic syndrome (MetS) is a group of at least three of the following metabolic disorders: central obesity, elevated glycaemia, high serum triglycerides, low serum high-density lipoprotein (HDL), and high blood pressure.

Definitions of metabolic syndrome have been proposed by the National Cholesterol Education Program - Panel III for the Treatment of Adults (NCEP - ATP III), the International Diabetes Federation (IDF), and the World Health Organization (WHO). In all of them, the main focus in defining the metabolic syndrome is on the five major medical conditions: abdominal obesity / waist circumference, high blood pressure, elevated fasting glycemia, elevated triglycerides, and low serum HDL. They are also used by health professionals as guidelines for diagnosing metabolic syndrome.

Carotid artery disease (CAD) involves changes in the arterial wall that cause IMT to thicken, narrow, or completely obstruct the carotid artery lumen. CAD can be caused by atherosclerosis as the most common cause, as well as other non-atherosclerotic causes such as carotid dissection, fibromuscular dysplasia, arteritis (Takayasu), radiation, glomus tumors on bifurcation and trauma. Carotid bifurcation is particularly predisposed to atherosclerosis due to its unique hemodynamics - impaired laminar flow. Carotid bifurcation plaques often extend to the initial ACI and ACE sections.

In addition to carotid bifurcation, another predilection site for atherosclerosis is the ostium of the ACI, including the posterior outer wall of the carotid sinus, and often extending into the distal common carotid artery (ACC).

Asymptomatic CAD passes without clinical manifestation of brain injury. While symptomatic CAD may manifest clinically as transient ischemic attack (TIA) or cerebrovascular insult (CVI). Atherosclerotic plaques can rupture and form emboli that can obstruct any of the intracranial arteries (causing TIA or CVI) or invade the retinal arteries (causing amaurosis fugax or retinal ischaemia). CVI is a medical condition in which poor blood flow to the brain results in cell death by initiating an ischemic cascade [1]. By definition of the American Heart Association and the American Stroke Association (AHA / ASA) in 2009, TIA is a transient episode of vascular neurological dysfunction caused by focal cerebral, spinal, or retinal ischemia with no evidence of acute cerebral infarction [2].

The declining phenomenology of CVI and TIA depends on which part of the brain is involved in ischemic suffering.

Namely, the risk of carotid artery disease, cardiovascular disease, diseases related to the deposition of fat in the arterial walls and stroke is higher in individuals with metabolic syndrome [3,4].

Generalized atherosclerosis has been shown to be associated with carotid atherosclerosis, which can be successfully detected using a non-invasive diagnostic method such as ultrasonography. There is abundant data on the independent association between the individual components of Metabolic Syndrome and vascular structure and function [5,6], which are also recognized as independent predictors of adverse cardiovascular events [7].

The more components of the risk factors that make up the metabolic syndrome are present, the greater the risk and mortality from cardiovascular disease [8].

Objective: To determine the impact of the number of MetS components on CAD.

Material and methods

This analytical unicenteric cross-sectional study included 80 subjects with MetS. The criteria for the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) were used to diagnose MetS, which implies the presence of at least three of the following five components:

1. Abdominal obesity - increased waist circumference in men ≥ 102cm (40 in), in women ≥ 88 cm (35 in)
2. Elevated triglycerides ≥ 150 mg/dL (1.69 mmol/L), or treatment for elevated triglycerides (e.g. fibrates or nicotinic acid)
3. Decreased HDL cholesterol levels in men <40 mg/dL (1.03 mmol/L), women <50 mg/dL (1.29 mmol/L), or treatment for HDL cholesterol lowering drugs (e.g. fibrates or nicotinic acid)
4. Elevated blood pressure: systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg; or drug treatment for hypertension
5. Elevated fasting blood glucose over 100 mg/dL (5.6 mmol/L); or drug treatment for elevated glycaemia

CAD was diagnosed with the Esaote My Lab70 HVG device, with a linear probe (7.5 MHz), according to the Ultrasound consensus criteria for CAD of the Association of Radiologists (2002, San Francisco).

Table 1. Ultrasonographic assessment of CAD according to ultrasound consensus criteria for carotid stenosis

Degree of stenosis	**Structural finding**	**PSV - Peak Systol velocity**	**ACI/ACC PSV ratio**	**End diastole velocity - EDV**
I Absence of stenosis Normal finding	**IMT normal, Without plaques**	**<125 cm/s**	**<2**	**<40 cm/s**
II Stenosis <50%	**IMT thickened, Visible plaque < 50%**	**<125 cm/s**	**<2**	**<40 cm/s**
III Stenosis 50 - 69%	**IMT thickened, Visible plaque > 50%**	**125 – 230 cm/s**	**2 – 4**	**40 – 100 cm/s**
IV Stenosis 70% to subocclusion (up to 99%)	**Visible narrowing >50%**	**>230 cm/s**	**>4**	**>100 cm/s**
V Subocclusion / almost occlusion	**Markedly visible narrowing; almost obliterated a.**	**It may be low or undetectable**	**Variable**	**Variable**
VI Occlusion	**No flow, the lumen is visible**	**No flow, undetectable**	**Not applicable**	**Not applicable**

Results

CAD was diagnosed in 77 (96.25%) EG subjects, and only 3 subjects (3.75%) were without CAD. (Chart 1).

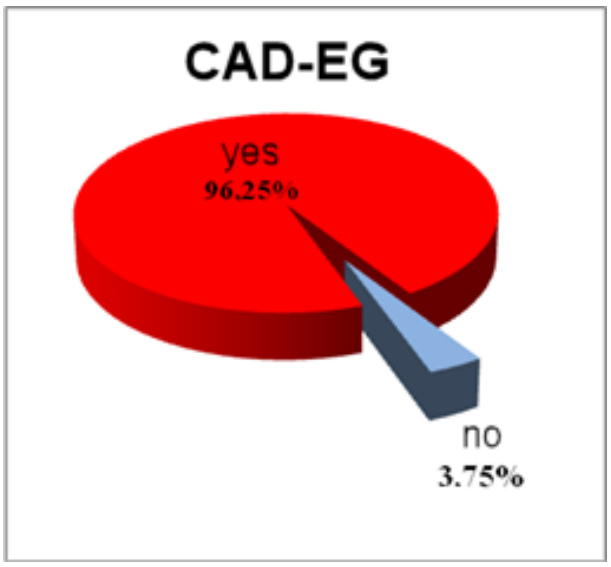


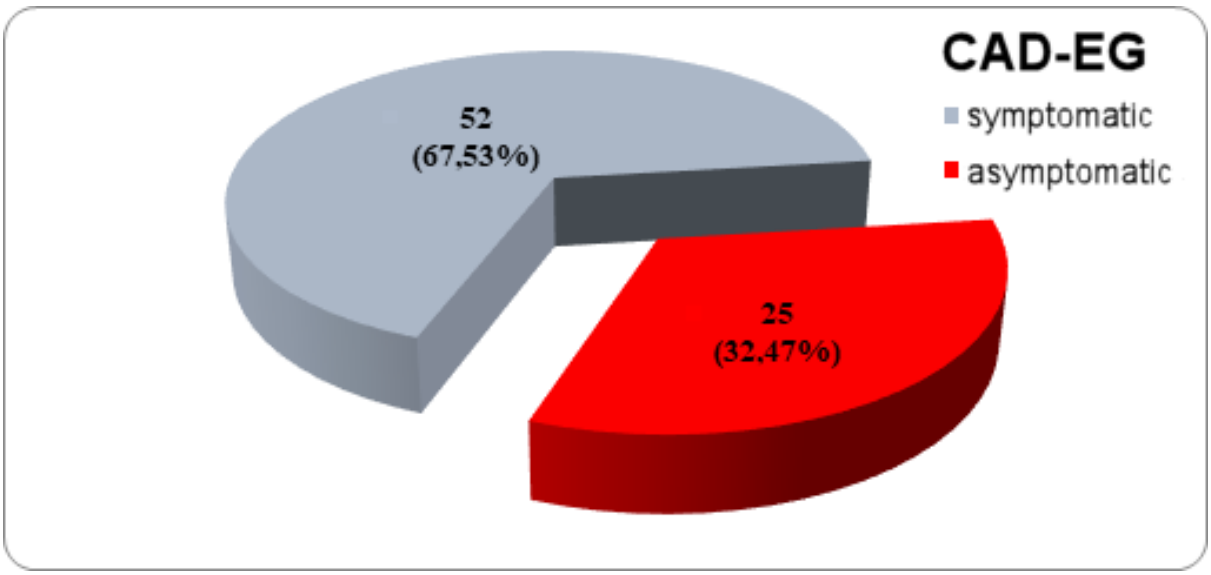
Chart 1. Representation of CAD in EG

Carotid artery disease was symptomatic in 52 (67.5%) EG subjects, while 25 (32.47%) EG subjects were registered with asymptomatic CAD. (Table 2, Chart 2).

Table 2. Frequency of symptomatic and asymptomatic CAD in EG

CAD	**EG** **n (%)**
Symptomatic	52 (67.53)
Asymptomatic	25 (32.47)

EG – subjects with metabolic syndrome



Graph 2. Prevalence of symptomatic and asymptomatic CAD in EG

The distribution of subjects from the study group in terms of the number of metabolic risk factors, shows that the most common were subjects with 4 risk factors - 34 (42.5%), followed by 24 (30%) subjects with 3, and 22 (27.5%) subjects with 5 metabolic risk factors (Table 3).

Table 3. The distribution of subjects from the study group in terms of the number of metabolic risk factors

EG	
number of factors	**n (%)**
3	24 (30)
4	34 (42.5)
5	22 (27.5)

According to the results shown in Table 4, 3 metabolic risk factors were present in 15 (62.5%) female and 9 (37.5%) male subjects, 4 risk factors in 19 (55.9%) female and 15 (44, 1%) male subjects, 5 metabolic risk factors were equally registered in both genders 11 (50%).

Table 4. Gender distribution in EG subjects with 3,4 and 5 components of MetS

Group	Gender	Number of factors				p value
		N	3	4	5	
			n (%)	n (%)	n (%)	
EG	Female	41	15 (62.5)	15 (44.12)	11 (50)	X^2=1.92
	Male	39	9 (37.5)	19 (55.88)	11 (50)	p=0.38 ns

EG – subjects with metabolic syndrome X^2 (Chi-square test)

No statistically significant difference was found between female and male subjects with metabolic syndrome in terms of the number of metabolic risk factors (p = 0.38).

Regarding the age distribution, the subjects from EG with 4 metabolic risk factors had the lowest average age (67.7 ± 7.9), followed by the subjects with 3 risk factors (68.7 ± 9.7) and with 5 metabolic risk factors (69.6 ± 8.6), but without statistically significant difference (p = 0.72), (Table 5).

Table 5. Age distribution of EG subjects with 3, 4 and 5 components of MetS

Group	Number of factors	Descriptive statistics (age)		p value
		N	mean ±SD	
EG	3	24	68.7 ± 9.7	F=0.34
	4	34	67.7± 7.9	p=0.72 ns
	5	22	69.6± 8.6	

EG – subjects with metabolic syndrome F (Analysis of Variance)

The results of the statistical analysis of the prevalence of CAD in EG subjects with different number of MetS components showed that CAD was diagnosed in 21 (87.5%) subjects with 3 metabolic risk factors and in all subjects with 4 and 5 risk factors. This statistically confirmed that the subjects with a lower number of risk factors for metabolic syndrome have significantly less carotid artery disease (p = 0.026), (Table 6, Graph 3).

Table 6. Prevalence of symptomatic and asymptomatic CAD in EG subjects with different number of MetS components

Group	Variable	Number of factors				p value
		N	3 n (%)	4 n (%)	5 n (%)	
EG	**CAD**					
	Yes	77	21 (87.5)	34 (100)	22 (100)	X^2=7.27
	No	3	3 (12.5)	0	0	p=0.026 sig
	CAD–symptomatic					
	Yes	52	13 (61.9)	22 (64.71)	17 (77.27)	X^2=1.4
	No	25	8 (38.1)	12 (35.29)	5 (22.73)	p=0.5ns

EG – subjects with metabolic syndrome X^2 (Chi-square test); sig p<0.05

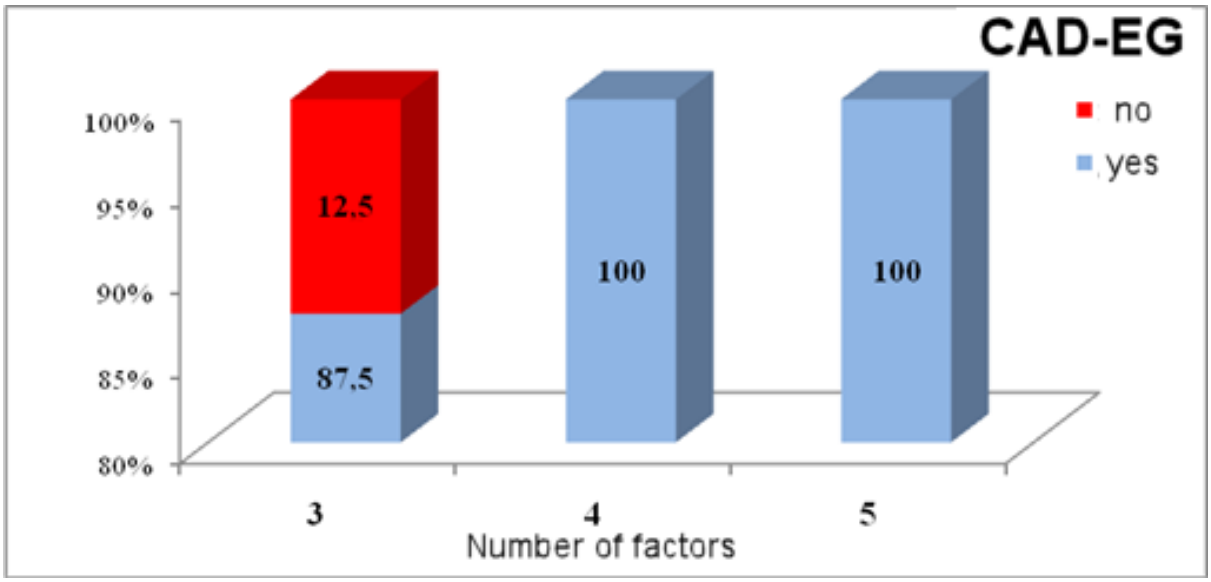


Chart 3. Percentage distribution of EG subjects with and without CAD in relation to the number of MetS components

The results of the statistical analysis of the prevalence of symptomatic CAD in subjects from EG with different number of components of MetS showed the presence of symptomatic CAD in 13 (61.9%) subjects with 3 metabolic risk factors, in 22 (64.7%) with 4 risk factors, and in 17 (77.3%) with 5 risk factors (Table 6).

Subjects with and without CAD differed significantly in terms of the number of metabolic risk factors as components of MetS (p = 0.026), (Table 6).

The number of metabolic risk factors did not differ significantly in EG subjects with symptomatic and asymptomatic CAD (p = 0.5). All 5 risk factors were present in 5 (20%) subjects with asymptomatic and 17 (32.7%) subjects with symptomatic CAD (Table 7).

Table 7. Prevalence of symptomatic and asymptomatic CAD in EG by number of MetS components

examined group				
Number of factors	**CAD symptomatic**			**p value**
	N	**No**	**Yes**	
		n (%)	**n (%)**	
3	21	8 (32.0)	13 (25)	X^2=1.4
4	34	12 (48.0)	22 (42.31)	p=0.5 ns
5	22	5 (20)	17 (32.69)	

EG – subjects with metabolic syndrome X^2 (Chi-square test)

All 5 metabolic risk factors were present more often in the EG subjects with symptomatic CAD than the subjects with asymptomatic CAD, but without confirmed statistically significant difference in 17 (32.7%) vs 5 (20%), p = 0.25, (Table 8).

Table 8. Representation of EG subjects with symptomatic and asymptomatic CAD with all 5 components of MetS

EG				
12345	**CAD symptomatic**			**p value**
	N	**Yes**	**No**	
		n (%)	**n (%)**	
< 5 components	55	35 (67.31)	20 (80.0)	X^2=1.3
= 5 components	22	17 (32.69)	5 (20.0)	p=0.25ns

EG – subjects with metabolic syndrome X^2 (Chi-square test)

1. Abdominal obesity - increased waist circumference in men ≥ 102cm (40 in), in women ≥ 88 cm (35 in)
2. Elevated triglycerides ≥ 150 mg/dL (1.69 mmol/L), or treatment for elevated triglycerides (e.g. fibrates or nicotinic acid)
3. Decreased HDL cholesterol levels in men <40 mg/dL (1.03 mmol/L), women <50 mg/dL (1.29 mmol/L), or treatment for HDL cholesterol lowering drugs (e.g. fibrates or nicotinic acid)
4. Elevated blood pressure: systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg; or drug treatment for hypertension
5. Elevated fasting blood glucose over 100 mg/dL (5.6 mmol/L); or drug treatment for elevated glycaemia

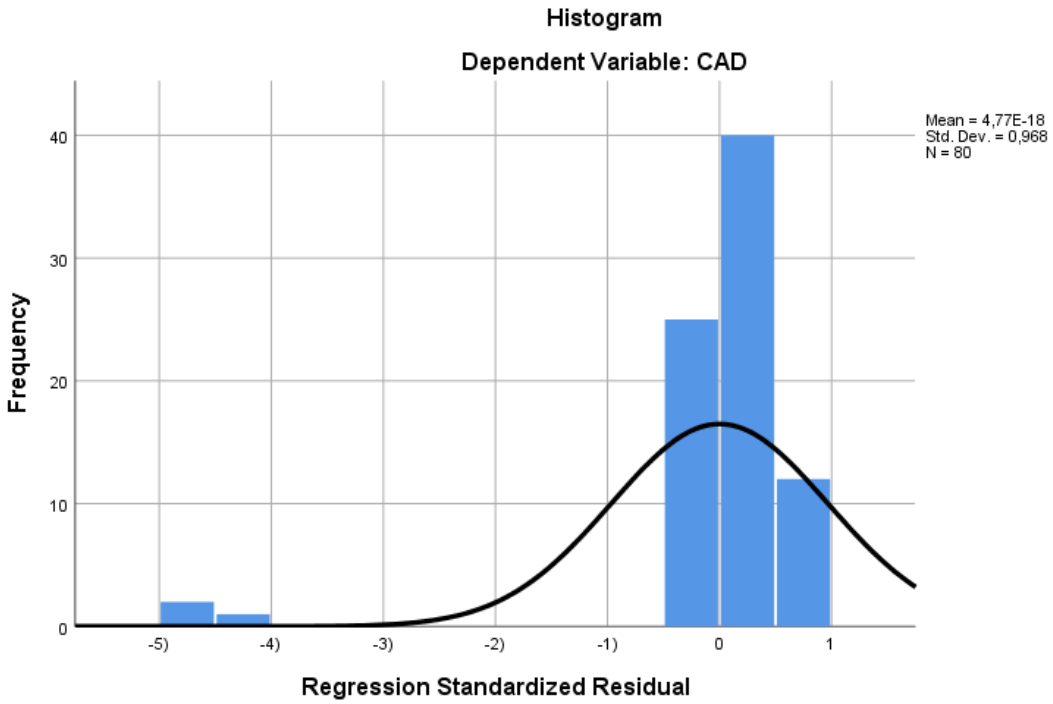


Chart 4. Regression analysis histogram of dependent variable CAD

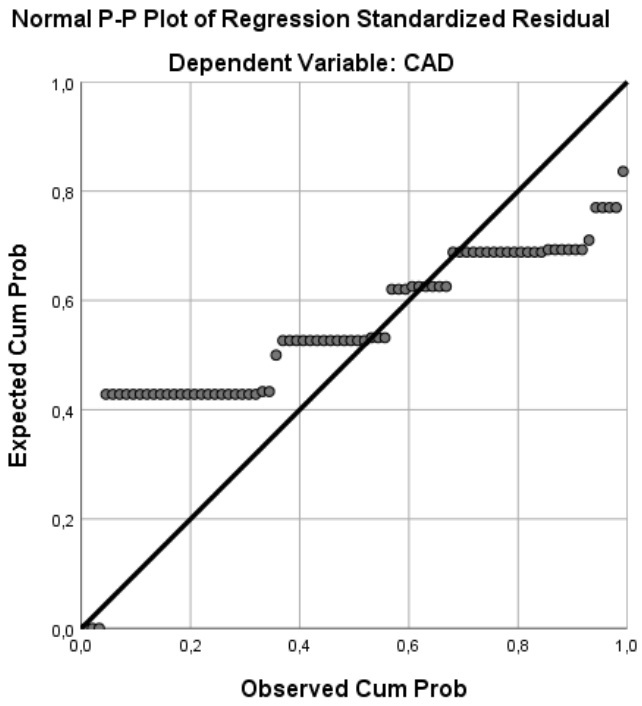


Chart 5. Normal P-P plot of regression standardized residual dependent variable CAD

Table 9. Regression analysis coefficients

Coefficients[a]

Model	Unstandardized Coefficients		Standardized Coefficients			95,0% Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
(Constant)	,735	,218		3,364	,001	,299	1,170
Waist circumference in examined group	,126	,046	,315	2,752	,007	,035	,217
Increased triglicerides and/or treatment in examined group	,091	,063	,171	1,444	,153	-,035)	,217
Increased HDL cholesterol and/or treatment in examined group	,002	,052	,005	,047	,963	-,102)	,107
Hypertension and/or treatment in examined group	,034	,190	,020	,178	,859	-,345)	,413
Hyperglicemia and/or tretment in examined group	,046	,049	,109	,947	,347	-,051)	,144

a. Dependent Variable: CAD

Based on the results shown in Table 9, Waist circumference in examined group has independent significant impact on CAD (p=0.001).

Discussion:

In recent years, the attention of the world medical community has increasingly turned to the MetS and its negative effects on human health. This is further boosted by worldwide statistics showing a growing trend in the number of people with MetS. According to the Third National Health and Nutrition Survey (NHANES III), approximately 47 million people in the United States have MetS, and 44% of subjects are 50 years of age or older [9,10]. Approximately 24% of the adult population in the United States has MetS.

In recent years there has been increasing evidence of the impact of metabolic syndrome on the onset and progression of atherosclerosis and an increased risk of developing carotid artery disease, cardio and cerebrovascular disease, diabetes mellitus.

Atherosclerosis is the most common pathological disorder in CAD characterized by pathological thickening of the arteries and plaque formation. In fact, the carotid artery is the fourth most common vessel affected by atherosclerosis, after the abdominal aorta, coronary, and popliteal artery [11].

According to the National Heart, Lung, and Blood Institute - NHLBI, as well as numerous studies, people with metabolic syndrome are twice as likely to have heart disease, three times more likely to have a heart attack or stroke, and five times more likely to develop diabetes, compared with people without metabolic syndrome [12].

Higher prevalence of CAD in MetS subjects was also shown by the results of several studies that determined carotid atherosclerosis by determining arterial stiffness, [13] the appearance of carotid plaques [14], or by measuring IMT [15].

Also, the study by Angelo Scuteri et al., which included 471 subjects from the Baltimore Longitudinal Study on Aging, aimed to evaluate whether the grouping of metabolic risk factors in MetS has a greater effect on vascular parameters (vascular thickening and stiffness) than the effect of individual metabolic factors outside the MetS. Vascular parameters were determined by extracranial ultrasonographic examination of the carotid arteries. The results of their study showed that MetS leads to disproportionate growth of carotid IMT (+ 16%, $p < 0.0001$) and stiffness (+ 32%, $p < 0.0001$), compared with the control group without MetS and with individual metabolic risk factors.

These results suggest a strong synergistic effect of MetS components on the occurrence of CAD, which is manifested by an increase in the analyzed vascular parameters [16].

The Botnia study examined the risk of stroke and cardiovascular risk associated with MetS in 4483 subjects. In multiple logistic regression analysis, MetS was an independent significant risk factor for stroke (RR 2.3, $P < 0.001$ compared with subjects without MetS).

The results of this study showed that none of the individual components of MetS were significantly associated with stroke risk [17]. Also, NHANES III, which included 10,000 subjects, showed a significant association of MetS with stroke, compared with subjects without MetS [18].

Olijhoek JK et al, in their cross-sectional study examined whether MetS was associated with advanced vascular damage in patients with coronary artery disease, stroke, peripheral arterial disease, or abdominal aortic aneurysm. They concluded that in patients with manifested atherosclerotic vascular disease, an increase in the number of MetS components was also associated with an increase in surrogate markers of vascular damage [19].

The results of this cross-sectional study are in accordance with the data from the literature and the results of the research, i.e. a significant association of MetS with CAD has been confirmed as a significant risk factor for CVI and TIA. According to the obtained results, CAD was diagnosed in 77 (96.25%) subjects from the examined group, and only 3 subjects (3.75%) were without CAD. This statistical result suggests that carotid artery disease is significantly associated with metabolic syndrome.

In the examined group 52 (67.5%) subjects had symptomatic CAD, and only 25 (32.47%) subjects had asymptomatic CAD.

This reaffirms and supports the fact that the grouping of metabolic risk factors in MetS has great clinical significance in identifying a vulnerable population with CAD as a significant risk factor for CVI and TIA and their timely and adequate primary and secondary prevention.

A large cross-sectional study of the MetS and CAD association has been conducted in northern China. It covered a total of 8,833 Chinese from the Jidong and Kailuan communities, aged 40 or older, between 2010 and 2014. The presence of CAD was determined by ultrasonographic examination of the extracranial segment of the carotid artery basin.

The results of this study showed that subjects with MetS were at increased risk of CAD compared to those without MetS, and that the increase in the number of MetS components increased the risk of CAD [20].

Alina S Kerimkulova et al, conducted a study in which the objective of the study was to determine whether there is an association between IMT of the extracranial segment of the carotid artery and the metabolic syndrome in ethnic Kyrgyz. The study included a sample of 144 respondents (69 men, 75 women) aged 36-73 years (mean age 51.03 ± 8.2). The results showed that the increase in IMT value was associated with an increase in the number of MetS components [21].

Ryuichi Kawamoto et al., From Japan, published a study investigating whether MetS potentiates the increase in LDL-cholesterol associated with carotid atherosclerosis (22). The study included 760 patients (340 men aged 64 ± 16 years and 420 women aged 69 ± 13 years) in the medical department of Nomura Municipal Hospital in Seiyo. They determined the IMT in B mode ultrasonography and found that carotid IMT increased with increasing number of MetS components (p for trend <0.001). This suggests that MetS components synergistically affect carotid IMT as a marker of preclinical atherosclerosis.

In this study, statistical analysis of the prevalence of CAD in EG subjects with different numbers of MetS components showed that CAD was diagnosed in 21 (87.5%) subjects with 3 metabolic risk factors and in all subjects with 4 and 5 risk factors. This statistically confirmed that the subjects with a lower number of risk factors for metabolic syndrome have significantly less carotid artery disease (p = 0.026). The results of this study correspond to the results of the available research [20-22].

Conclusion:

This study clearly indicates that increasing the number of MetS components through their synergistic effect has a greater impact on the occurrence and progression of CAD.

This suggests that grouping metabolic risk factors into MetS and identifying individuals with MetS and their timely ultrasonographic extracranial carotid evaluation may be an important early marker for recognizing carotid atherosclerosis associated with an increased risk of cerebrovascular events in MetS.

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