RELATIONSHIP BETWEEN THE MEATABOLIC SYNDROME AND THE INDIVIDUAL METABOLIC RISCK FACTORS AND SYMPTOMATIC AND ASYMPTOMATIC CAROTID ARTERY DISEASE: IS THE WHOLE LARGER THAN ITS PARTS

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Abstract

Metabolic syndrome (MetS) is a group of at least three of the following metabolic risk factors: central obesity, elevated glycaemia, high serum triglycerides, low serum high-density lipoprotein (HDL), and high blood pressure. Atherosclerosis is the most common cause of extracranial CAD. It may be asymptomatic and symptomatic with clinical presentation of cerebrovascular insult (CVI) and transient ischemic attack (TIA).

Aim: to determine the relationship between MetS as a whole compared to individual metabolic risk factors and CAD.

This analytical unicentric cross-sectional study included 160 subjects divided into two groups: 80 subjects with MetS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria in the examined group (EG) and 80 subjects who have 1 or 2 individual metabolic risk factors and do not meet the diagnostic criteria for MetS in the control group (CG).

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). CAD was significantly more frequently diagnosed in 77 (96.25%) EG subjects, compared to 34 (42.5%) CG subjects (p <0.0001). In EG symptomatic CAD had 52 subjects (67.5%) compared to only 2 (5.9%) subjects in CG. With asymptomatic CAD were 25 (32.47%) EG and 32 (94.12%) CG subjects, which was statistically confirmed as significant (p <0.0001).

MetS is significantly associated with CAD, which is of cardinal importance for primary and secondary prevention of CVI and TIA.

Keywords: metabolic syndrome, carotid artery disease, cerebrovascular insult, transient ischemic attack

Introduction

Metabolic syndrome has recently attracted the attention of the medical scientific community and has become one of the major public health challenges worldwide [1,2]. But it is undeniable that the concept of an interrelated group of metabolic abnormalities has been known and recognized for decades, which is often present in people who develop cardiovascular disease and/or type 2 diabetes mellitus (DM). In 1999, the WHO defined the syndrome and changed its name to metabolic syndrome [3]. In 2001, the National Cholesterol Education Program - Adult treatment Panel III (NCEP-ATP III) proposed diagnostic criteria for metabolic syndrome and cut-off points for its components [4].

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), high blood pressure.

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

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 [5,6].

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.

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.

Atherosclerosis is the most common cause of CAD. It is a chronic, progressive, immunoinflammatory, fibroproliferative disease that underlies many life-threatening conditions such as carotid artery disease, coronary artery disease, and peripheral arterial disease. [7, 8].

CAD may be asymptomatic and symptomatic with clinical presentation of cerebrovascular insult (CVI) and transient ischemic attack (TIA).

*Objective:*To determine the association of MetS as a whole with CAD, compared to individual metabolic risk factors as its components.

Material and Methods

This study is designed by analytical unicentric cross-sectional study, which includes 160 subjects, divided into two groups: 80 subjects with MetS in the examined group (EG) and 80 subjects with 1 and / or 2 individual metabolic risk factors , but do not meet the diagnostic criteria for MetS in the control group (CG).

The criteria for the National Cholesterol Education Program, 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 Systole velocity	ACI/ACC PSV ratio	EDV End diastole velocity -
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 in 34 (42.5%) CG subjects. The more common frequency in subjects with CAD and EG was confirmed statistically significant for p <0.0001. This statistical result suggests the conclusion that the metabolic syndrome is significantly associated with CAD (Table 2, Charts 1 and 2).
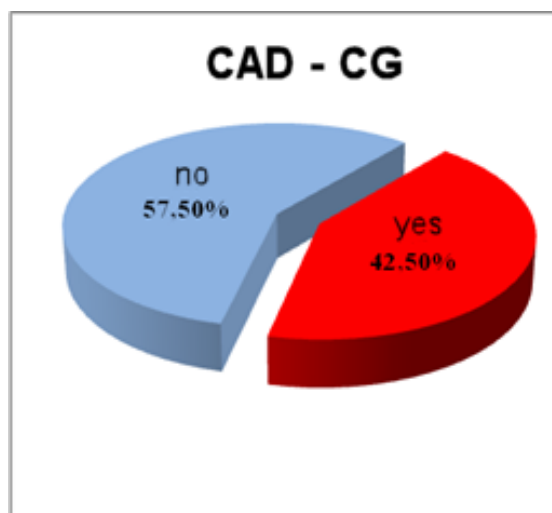
Table 2. Frequency of CAD in both groups

CAD	Group			p value
	N	EG n (%)	CG n (%)	
Yes	111	77 (96.25)	34 (42.5)	X^2=54.39
No	49	3 (3.75)	46 (57.5)	p=0.00000 sig

EG – subjects with metabolic syndrome X^2 (Chi-square test); sig p<0.05
CG – subjects without metabolic syndrome
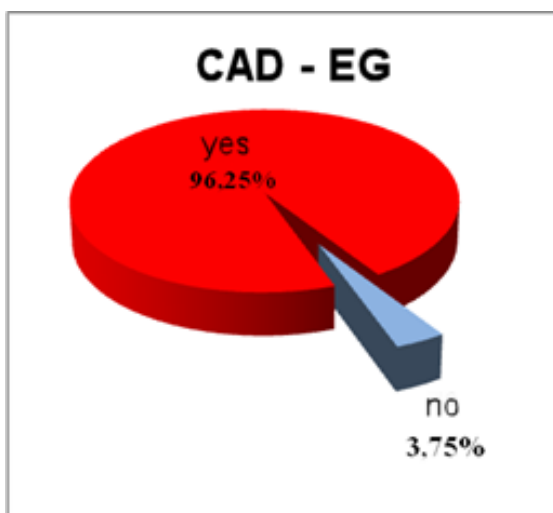
Chart 1. Frequency of CAD in EG group

Chart 2. Frequency of CAD in CG group

Regarding the gender distribution, the results of the statistical analysis showed that the gender of the subjects from the examined and control group had no significant effect on the frequency of CAD (p = 0.085, p = 0.58, respectively); CAD was diagnosed in 38 (49.35%) female and 39 (50.65%) male EG subjects, and in 22 (64.7%) female and 12 (35.3%) male CG subjects (table 3).

Table 3. Gender distribution of subjects with and without CAD in both groups

Group	Gender	CAD			p value
		N	Yes n (%)	No n (%)	
EG	Female	41	38 (49.35)	3 (100)	X^2=2.96
	Male	39	39 (50.65)	0	p=0.085 ns
CG	Female	49	22 (64.71)	27 (58.7)	X^2=0.29
	Male	31	12 (35.29)	19 (41.3)	p=0.58ns

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

CG – subjects without metabolic syndrome

In terms of age distribution, EG subjects with and without CAD did not differ significantly from their mean age (68.7 ± 8.4 vs. 64.3 ± 15.0; p = 0.39) (Table 4).

Table 4. Age distribution of subjects with and without CAD in both groups

| Group	CAD	descriptive statistics (age)		p value
		N	mean ±SD	
EG	Yes	77	68.7 ± 8.4	t=0.86
	No	3	64.3 ± 15.0	p=0.39ns
CG	Yes	34	66.2 ± 8.6	t=6.11
	No	46	50.6 ± 12.9	p=0.000000 sig

EG – subjects with metabolic syndrome   t (Student t-test for independent samples); sig p<0.05
CG – subjects without metabolic syndrome

Subjects from CG with CAD were of average age of 66.2 ± 8.6 years, while the subjects without CAD were of average age of 50.6 ± 12.9 years, the difference of 15.6 years was statistically confirmed as significant for p <0.0001, (Table 4, Chart 3).
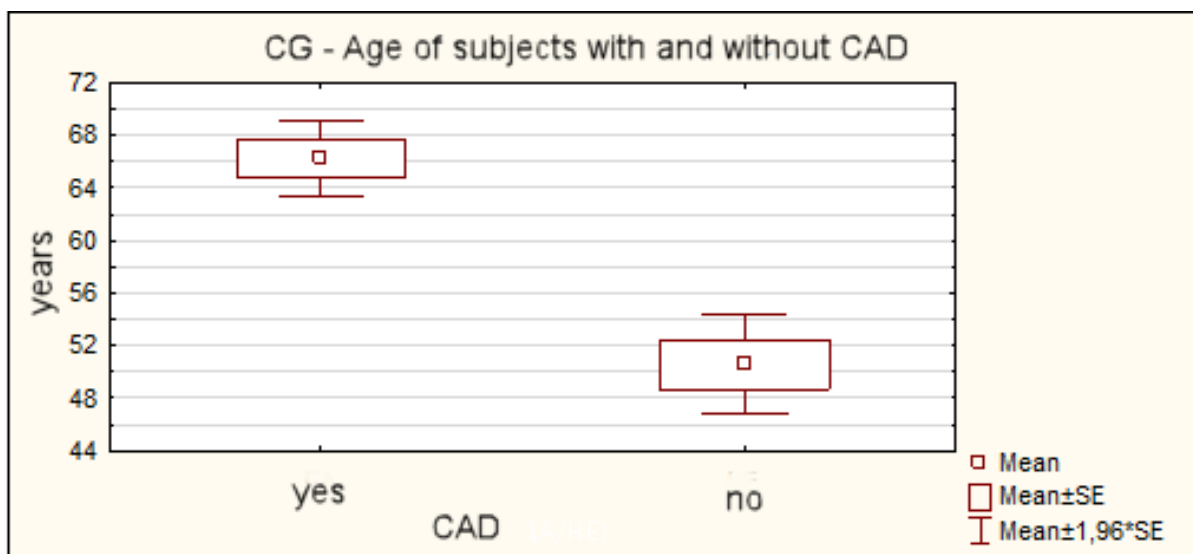
Chart 3. Age distribution among CG subjects with and without CAD

Carotid artery disease was symptomatic in 52 (67.5%) subjects from EG, and in only 2 (5.9%) subjects from CG, while with asymptomatic CAD 25 (32.47%) EG subjects were registered and 32 (94.12%) from CG.

The more frequent finding of symptomatic CAD in the subjects from EG compared to the subjects from CG, and the more frequent finding of asymptomatic in the subjects from CG was statistically confirmed as significant (i.e. p <0.0001) (Table 5, Chart 4).

Table 5. Frequency of symptomatic and asymptomatic CAD in both groups

CAD	Group			p value
	N	EG n (%)	CG n (%)	
Symptomatic	54	52 (67.53)	2 (5.88)	X^2=38.7
Asymptomatic	57	25 (32.47)	32 (94.12)	p=0.00000 sig

EG – subjects with metabolic syndrome
CG – subjects without metabolic syndrome

X^2 (Chi-square test); sig $p<0.05$
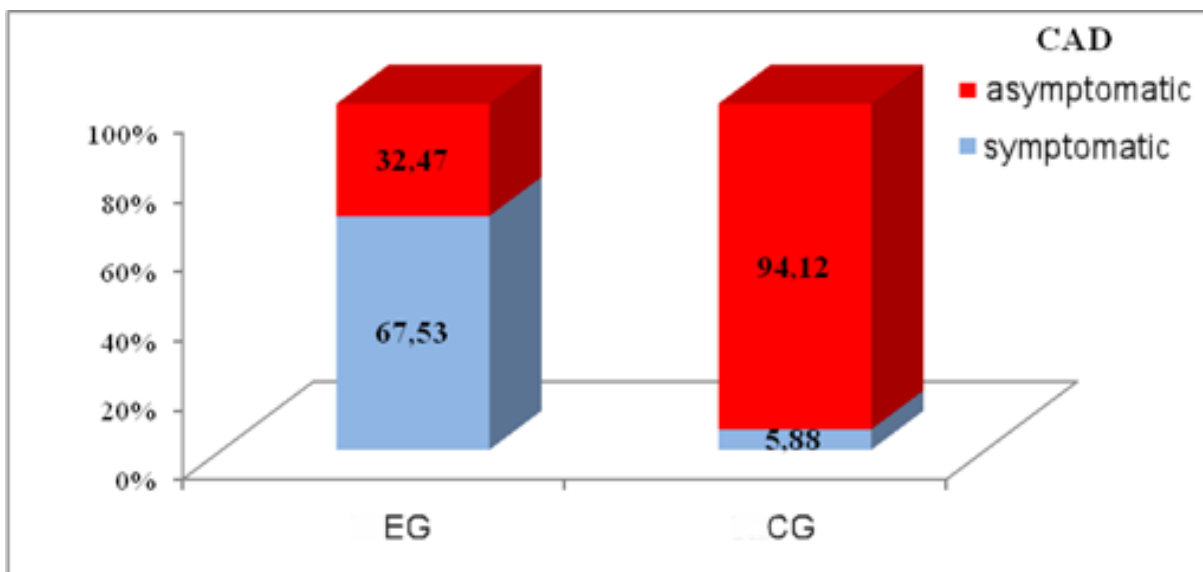
Graph 4. Frequency of symptomatic and asymptomatic CAD in both groups

In subjects with symptomatic CAD from EG, CVI or TIA were diagnosed insignificantly differently in female and male subjects (p = 0.89). CVI had 20 (47.7%) female and 22 (52.4%) male subjects, TIA was equally registered in female and male subjects from EG 5 (50%) (Table 6, Chart 7).
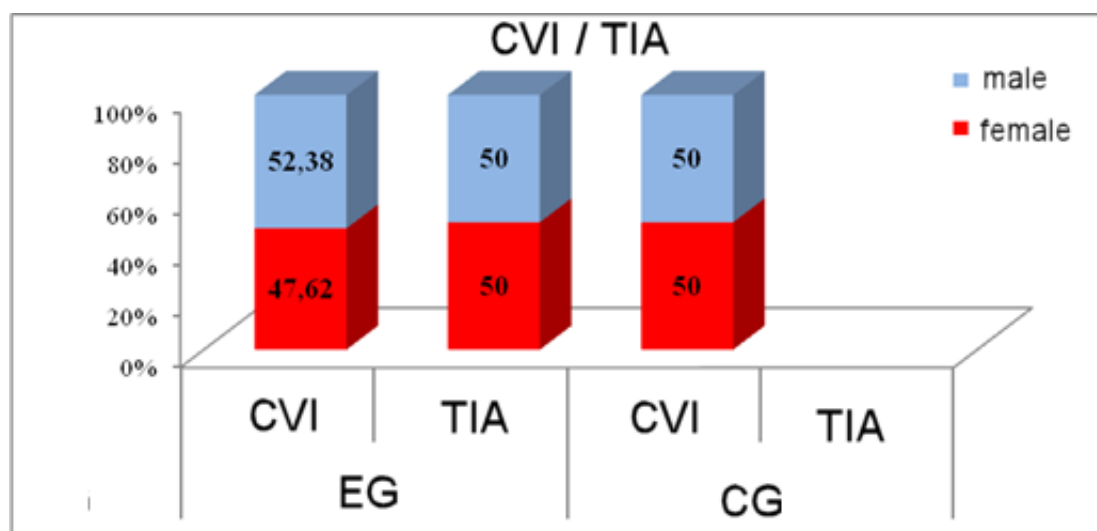
Among the subjects with symptomatic CAD from CG, 2 subjects had CVI, one female and one male (Table 6, Chart 7).

Table 6. Frequency of CVI and TIA in subjects with symptomatic CAD in both groups in both genders

Group	Gender	CVI / TIA			p value
		n	CVI n (%)	TIA n (%)	
EG	Female	25	20 (47.62)	5 (50)	X^2=0.018
	Male	27	22 (52.38)	5 (50)	p=0.89 ns
CG	Female	1	1 (50)		
	Male	1	1 (50)		

EG – subjects with metabolic syndrome X^2 (Chi-square test); sig p<0.05
CG – subjects without metabolic syndrome

Graph 7. Frequency of CVI and TIA in subjects with symptomatic CAD in both groups in both genders

Regarding the age distribution, the statistical analysis did not confirm a significantly different mean age of the subjects with CVI and TIA from EG (68.8 ± 9.1 and 67.8 ± 8.9 years, respectively; p = 0.75), and from CG, both subjects had CVI at the ages of 64 and 74 (Table 7).

Table 7. Age distribution among subjects from both groups with CVI and TIA

Group	CVI / TIA	descriptive statistics (age)		p value
		n	mean ±SD	
EG	CVI	42	68.8 ± 9.1	t=0.32
	TIA	10	67.8 ± 8.9	p=0.75ns
CG	CVI	2	64 and 74	

EG – subjects with metabolic syndrome   t (Student t-test for independent samples)
CG – subjects without metabolic syndrome

Discussion

According to current scientific research, about 20-25% of the world's population suffers from MetS. CAD is a significant risk factor for CVI and TIA. Some researchers question the clinical benefits of MetS [9].

Namely, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) believe that MetS should not be the target of clinical identification and recommend focusing on the individual components of MetS. They argue that the grouping of metabolic risk factors into a syndrome has little clinical significance and believe that the main clinical focus should remain on individual metabolic risk factors.

This statement as clinically controversial was not accepted by the International Diabetes Federation (IDF), who point out that despite differences in definition, diagnostic criteria and insufficiently specified pathophysiological mechanism and etiology, MetS is a whole that should not be ignored, and its clinical acceptance and application will lead to better control of risk factors and their side effects on end organs.

Cesare Cuspidi et al, conducted a meta-analysis of population-based studies searched by Ovid MEDLINE, PubMed and Cochrane CENTRAL databases, examined the association of MetS and CAD by analyzing data on the thickness of atherosclerotic plaques and carotid IMT in patients without MetS. The results of this meta-analysis involving 19696 subjects (22.2% with MetS) from eight studies showed that MetS was associated with both ultrasonographic carotid damage phenotypes [10].

The study of 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 [11].

Xuelong Li et al, performed a meta-analysis of prospective cohort studies (16 studies involving 116496 subjects) on the association of MetS and CVI / TIA. The results of this meta-analysis showed that MetS may be an important risk factor for CVI / TIA, especially in women and those with ischemic stroke [12].

The results of this cross-sectional study on the percentage of symptomatic CAD in subjects with MetS differ from the results of other analyzed studies, i.e. it is in a higher percentage of prevalence. However, it must be noted that there is insufficient research on the distribution of symptomatic CAD in MetS subjects, and there is insufficient data in the available literature.

There is insufficient research on the association between MetS and asymptomatic CAD, especially with such extensive analysis of demographic, clinical, biochemical, and ultrasonographic features in subjects in both groups, with or without MetS. The association and impact of MetS on early atherosclerosis in terms of gender distribution was analyzed in the studies of Kawamoto R et al [13] and Iglseder et al [14].

Numerous other cross-sectional studies have confirmed the association of MetS with carotid IMT changes as a marker of preclinical asymptomatic atherosclerosis correlated with an increased risk of cardiovascular and cerebrovascular disease [11,15,16,17].

The results of this 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.

Conclusion

The results of this study help to find key answers to one of the critical questions about MetS: "What is the value of identifying this phenotype outside of recognizing and treating its components in recognizing CAD as a risk factor for CVI and TIA?"

The results of this study indicate that the clinical focus in early detection of CAD as a risk factor for CVI and TIA and their timely and adequate primary and secondary prevention is in identifying subjects with the coexistence of three or more metabolic factors according to NCEP ATP III MetS criteria, which would be missed if the focus were limited to one or two individual metabolic risk factors.

The association of MetS and CAD has predictive value in recognizing cerebrovascular risk.

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