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Original article

Association between metabolic syndrome and homocysteinemia in ischemic stroke

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Summary

Introduction. Stroke is one of the leading causes of morbidity and mortality worldwide. The relationship between metabolic syndrome (MetS) and homocysteinemia (Hcy) as risk factors for ischemic stroke (IS) is not completely clear. The aim of the study was to determine the frequency of MetS, serum level of Hcy and the frequency of hyperhomocysteinemia (HHcy), as well as their association in patients with IS.

Methods. The research included 53 subjects being in rehabilitation after IS and 40 subjects in the control group in rehabilitation due to the back pain problems aged 50-70 years. The diagnosis of the ischemic stroke was established by insight in the medical documentation. All subjects had to have a diagnosis of stroke confirmed by imaging (CT or MR of the endocranium). All subjects in the control group were excluded from the existence of previous stroke, myocardial infarction, angina pectoris and peripheral vascular disease. MetS was defined according to the joint statement from 2009.

Results. The frequency of MetS was significantly higher in patients with IS compared to the control group (88.7% vs. 70.0%, $p<0.05$). The level of Hcy and the frequency of HHcy were increased in the patients with stroke compared to the control group (15.0±5.50 μmol/L vs. 11.2±2.51 μmol/L, $p<0.01$ and 39.2% vs. 11.4%, $p<0.01$, respectively). Among patients with IS, those with MetS had higher frequency of HHcy (42.2% vs. 16.7%, $p<0.05$) and it increased with more individual components of MetS (11.1% in patients with 3 components, 36.8% in patients with 4 components and 64.7% in patients with 5 components, $p<0.05$). Hcy was also in positive correlation with serum triglyceride level.

Conclusion. Our results suggest that MetS and Hcy represent a significant risk factors for IS. It seems that there is an association between these risk factors in pathogenesis of the IS, but further analyses are needed to confirm this hypothesis.

Key words: ischemic stroke, metabolic syndrome, homocysteine, atherosclerosis, obesity

Introduction

Stroke is one of the leading causes of morbidity and mortality worldwide [1,2]. Metabolic syndrome (MetS) is a group of metabolic and hemodynamic disorders that multiplies risk of atherosclerotic cardiovascular diseases (CVD). Patients with MetS have several times higher morbidity and mortality from type 2 diabetes mellitus (DM2), stroke and myocardial infarction [3]. The presence of MetS also increases the risk of the recurrent stroke [4].

Most commonly described components of MetS are high blood pressure, dyslipidemia (high triglycerides (Tg) and low high-density lipoprotein cholesterol level (HDL)), insulin resistance (IR) with consequent hyperglicaemia and visceral obesity [3]. There were many different criteria for MetS diagnosis in the past but in 2009, criteria were internationally agreed [5].

Homocysteine (Hcy) is sulfur-containing amino acid derived from methionine. Folic acid, vitamins B12 and B6 have an important role in homocysteine-methionine metabolic cycle [6]. Many prospective studies established Hcy as an independent risk factor for CVD, including stroke [7]. It is estimated that 5-7% of whole population have mild to moderate hyperhomocysteinemia (HHcy) and the main reasons are vitamins deficiency, medication, kidney diseases and genetic disorders [8].

Interaction between MetS/IR and HHcy has been described, but nature of that link has not yet been established well and data of many studies are conflicting [9-14]. Some authors even suggest that HHcy should be an additional constituent of MetS [6].

In a study of Meigs patients with DM2, as well as experimental animals with IR, had HHcy which was associated with changes in key enzymes of Hcy metabolism. It is supposed that methionine elimination stimulated by insulin could explain these findings [15]. Homocysteine-thiolactone, active form of Hcy, inhibits insulin-induced tyrosine phosphorylation of beta-subunit insulin receptors and its substrate: insulin receptor substrate 1 and p60-70 in rat liver cells [10]. Paterson et al. showed that Hcy dose-dependently inhibits insulin releasing in pancreatic beta cells [16]. In insulin resistant experimental animals HHcy may be caused by hyperinsulinemia but Hcy may also cause IR through insulin receptor kinase inhibition. Thus, HHcy might be a cause or/and a result of IR [13]. The aim of this study was to determine the frequency of MetS, level of Hcy and frequency of HHcy, as well as their association, in patients with IS.

Methods

The cross-sectional study included 53 consecutive patients with IS recruited from the neurological department of the Institute of Physical Medicine and Rehabilitation ''Dr Miroslav Zotović'' in Banja Luka one to three months after the acute event. The study group consisted of 53 patients who had suffered an acute ischemic stroke, and were in rehabilitation at the above-mentioned Institute. The diagnosis of the disease was established by insight in the medical documentation. All subjects had to have a diagnosis of ischemic stroke confirmed by imaging (CT or MR of the endocranium). A control group consisted of 40 gender- and age-matched patients in rehabilitation due to degenerative spinal diseases hospitalized at the same time in the above-mentioned Institute. All subjects in the control group were excluded from the existence of previous stroke, myocardial infarction, angina pectoris and peripheral vascular disease by anamnesis and insight of previous medical documentation.

The waist circumference (WC) was measured in the horizontal plane at the midpoint between the last right rib and the iliac crest using an inelastic fiberglass tape. Blood pressure (BP) was measured by standard sphygmomanometer at least 10 minutes after rest. For each patient BP was measured in duplicate and mean value was used. Blood sample was collected after a 12-hour fasting period to determine HDL, Tg, glucose and Hcy levels. Enzymatic colorimetric method was used to determine glucose, HDL i Tg serum levels. Hcy serum level was measured by Chemiluminiscent microparticle immunoassay method (Architect Tacrolimus device, produced by Abbot Laboratories). Reference values for Hcy level in serum were defined by kit producer: 5.46 – 16.20 μmol/L for men and 4.44-13.56 μmol/L for women.

MetS was defined according to the joint statement from 2009 (5). At least three of five criteria are requested to fulfill diagnostic criteria:

1. Elevated waist circumference (≥ 94 cm for males and ≥ 80 cm for females);
2. Elevated Tg (≥ 1.7 mmol/L) or use of medication for hypertriglyceridemia;
3. Reduced HDL cholesterol (<1.0 mmol/L for males and <1.3 mmol/L for females);
4. Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥ 85 mmHg), diagnosis of hypertension or use of medication for hypertension;
5. Elevated fasting glucose (≥5.6 mmol/L) or use of medication for hyperglycemia.

Normality of data was tested by the Kolmogorov-Smirnov test. For group comparisons, chi-square test, Mann-Whitney U test and Student t-test were used, as appropriate. Correlations were assessed using Spearman's rho. Significant testing was two-sided, with alpha set to 0.05 for statistical significance and 0.01 for high statistical significance.

Results

Table 1 shows descriptive statistics parameters of age, parameters of MetS (WC, systolic and diastolic BP, glycaemia, Tg and HDL) and homocysteinemia for both groups, such as statistic parameters of LDL and total cholesterol for examined group.

Mean homocysteinemia value among patients was 15.04 μmol/L, vs. 11.16 μmol/L among controls (p<0.01) (Table 1). MetS was found among 88.7% patients with stroke and table 2 shows prevalence of HHcy among examined and control group. HHcy was present among 39.2% examinees and 11.4% controls and the diference was statisticly significant (p<0.01). Patients from the examined group with MetS had HHcy in 42.2% cases, while patients without MetS had HHcy in 16.7% cases. The diference wasn't statistically significant

Table 1. Descriptive statistics parameters

	Group	Number	Mean	SD	Min-Max				
Age	Patients	53	63.28	5.97	61.68	64.89			
	Controls	40	58.48	5.43	56.79	60.16			
WC	Patients	53	97.75	12.34	94.43	101.08			
	Controls	39	98.92	9.65	95.90	101.95			
Systolic blood pressure	Patients	53	135.85	12.62	132.45	139.25			
	Controls	39	138.72	18.49	132.92	144.52			
Diastolic blood pressure	Patients	53	80.75	7.30	78.79	82.72			
	Controls	39	85.38	8.22	82.80	87.97			
Glycaemia	Patients	53	5.86	1.76	5.39	6.33			
	Controls	40	6.06	1.98	5.45	6.68			
Total cholesterol	Patients	43	6.05	1.37	5.64	6.46			
	Controls	-	-	-	-				
HDL	Patients	53	0.90	0.21	0.84	0.95			
	Controls	40	1.43	0.41	1.30	1.56			
LDL	Patients	12	3.31	1.14	2.67	3.96			
	Controls	-	-	-	-				
Tg	Patients	53	1.77	0.86	1.53	2.00			
	Controls	40	1.96	2.10	1.31	2.61			
Hcy	Patients	51	15.04	5.50	13.53	16.55	***t***	***df***	***p***
	Controls	35	11.16	2.51	10.33	11.99	***4.420***	***75***	***<0.01***

WC – Waist Circumference, HDL - High Density Lipoprotein, LDL - Low Density Lipoprotein, Tg - Triglycerides, Hcy - Homocysteine

most likely because of small numbers of patients without MetS (Table 3).

Prevalence of HHcy was increasing with the numbers of MetS components in the examined group. Patients with three MetS components had HHcy in 11.1% cases, those with four MetS components in 36.8%, while patients with all five MetS components had HHcy in 64.7% cases ($p<0.05$) (Figure 1).

Table 2. Prevalence of HHcy among examined group and control group

HHcy	Patients		Controls		Total	
	Number	%	Number	%	Number	%
Yes	20	39.22	4	11.43	**24**	**27.91**
No	31	60.78	31	88.57	**62**	**72.09**
Total	**51**	**100.00**	**35**	**100.00**	**86**	**100.00**

c2	*df*	*p*
7.966	**1**	**0.005**

HHcy - Hyperhomocysteinemia

Table 3. Prevalence of HHcy in regard to MetS among examined group

HHcy in regard to MetS	Patients with MetS		Patients without MetS		Total	
	Number	%	Number	%	Number	%
Yes	19	42.22	1	16.67	20	39.22
No	26	57.78	6	83.33	32	60.78
Total	**45**	**100.00**	**6**	**100.00**	**51**	**100.00**

c2	*df*	*p*
1.450	**1**	**0.228**

HHcy - Hyperhomocysteinemia, MetS - Metabolic Syndrome

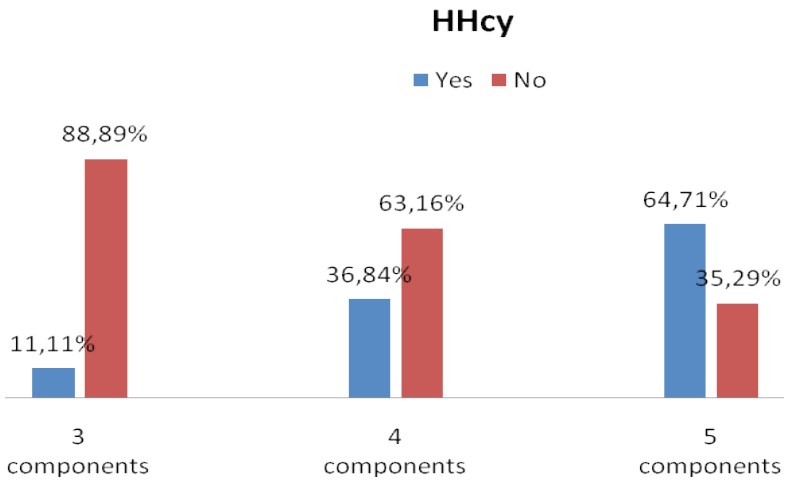

Figure 1. *HHcy prevalence in regard to number of MetS components in the examined group HHcy - Hyperhomocysteinemia, MetS - Metabolic Syndrome*

Table 4 shows Pearson's correlation of homocysteinemia with MetS components in the examined group. Homocisteinemia positively correlated with serum Tg level and it was statistically significant. Other MetS components had slightly positive correlation with Hcy, except HDL which had slightly negative correlation. These correlations weren't statistically significant.

Table 4. Pearson's correlation of homocisteinemia and MetS components

Pearson's correlation		Homocysteine	Waist circumference	Tg	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure	Glycemia
Homocysteine	***r***	1.000	0.125	***0.288***	-0.223	0.190	0.136	0.241
	p		0.382	***0.041***	0.116	0.183	0.340	0.089
Waist circumference	***r***	0.125	1.000	0.141	***-0.371***	0.229	***0.358***	0.139
	p	0.382		0.314	***0.006***	0.099	***0.009***	0.321
Tg	***r***	***0.288***	0.141	1.000	***-0.369***	0.075	0.062	0.001
	p	***0.041***	0.314		***0.007***	0.593	0.658	0.997
HDL cholesterol	***r***	-0.223	***-0.371***	***-0.369***	1.000	***-0.315***	***-0.366***	-0.075
	p	0.116	***0.006***	***0.007***		***0.022***	***0.007***	0.596
Systolic blood pressure	***r***	0.190	0.229	0.075	***-0.315***	1.000	***0.661***	***0.280***
	p	0.183	0.099	0.593	***0.022***		***0.000***	***0.042***
Diastolic blood pressure	***r***	0.136	***0.358***	0.062	***-0.366***	***0.661***	1.000	0.177
	p	0.340	***0.009***	0.658	***0.007***	***0.000***		0.205
Glycemia	***r***	0.241	0.139	0.001	-0.075	***0.280***	0.177	1.000
	p	0.089	0.321	0.997	0.596	***0.042***	0.205	

Tg - Triglycerides, HDL-High Density Lipoproteins

Discussion

Most of the examinees of the present cross-sectional study had several metabolic impairments and thus fulfilled criteria for MetS diagnosis. Prevalence of the MetS was high in both examined groups yet it was significantly higher in patients with IS (89% vs 70%).

The data from other studies about MetS prevalence are heterogeneous taking into account different criteria used for its diagnosis, as well as influence of the gender, age and ethnicity of the examined population on MetS diagnosis. In general population older than 20-25 years MetS prevalence in men in urban areas varies from 8% in India till 24% in the USA and from 7% in France till 43% in Iran in women. MetS prevalence in general population increases with aging and it amounts from 7% in the examinees aged 21-29 and 44% in the examinees aged 60-69 years in American population [17]. The frequency of MetS is even higher in patients with manifest atherosclerotic diseases. Olijhoek et al. found that 43% of patients with stroke met criteria for MetS diagnosis [18] while in a study of Reffat

et al. that percentage was 57% for all types of stroke and 64% for ischemic stroke [19]. In all of these studies NCEP ATP III criteria were used for MetS diagnosis [20]. In the present study we used more strict criteria for MetS diagnosis and data from other authors that used the same criteria are limited. That fact as well as older participants could explain higher prevalence of MetS in this study compared to previous studies. Low level of physical activity and sedentary lifestyle due to chronic back pain could contribute to high prevalence of MetS in the control group.

In the present study the examinees with IS had significantly higher value of homocysteinemia as well as three times higher prevalence of HHcy in comparison to the control group. Fallon et al. found that increase of homocysteinemia of 4.7 μmol/L increases the risk for IS of 20-40% in male smokers in Finland [21]. Many studies showed that Hcy is independent risk factor for atherosclerotic vascular diseases [6,7,11,12] while some authors found positive correlation between Hcy level and vascular dementia occurrence after IS [22].

We also analyzed the association between MetS and HHcy in the patients with stroke. HHcy was present in 42% of patients with MetS and only in 17% of patients without diagnosis of MetS. This difference was not significant most likely because of the small number of patients without MetS. As the number of MetS components increased, the frequency of HHcy also increased which further indicates the association between MetS and HHcy in patients with IS.

The data from literature about the association between MetS and homocysteinemia are conflicting and they are limited when it comes to agreed criteria for MetS diagnosis that we used. Some studies did not find any connection between Mets and Hcy levels [9,10] or even found inverse correlation between IR and homocysteinemia [23], but the majority of the studies found positive correlation of MetS or its components and Hcy [6,11,12,13,15,24,25,26]. Bellia et al. showed that 67% of patients with CVD had MetS and HHcy simultaneously. The authors supposed that MetS could be significant pathogenetic factor through which HHcy induces vascular damage and increases CVD risk [27]. In Framingham's study HHcy had moderate positive correlation with hyperinsulinemia and serum Hcy levels were significantly higher in examinees with three or more MetS components compared with those without MetS or with single MetS component [15]. Setola et al. lowered Hcy and insulin serum levels and improved insulin sensitivity and endothelial function in patients with MetS by prolonged treatment with folic acid and vitamin B12 [28]. HHcy and MetS interact in atherosclerotic vascular diseases by promotion of oxidative damage, endothelial cell dysfunction, increased platelets aggregation, etc. [6,24,25,26].

When it comes to the correlation of MetS single components and homocysteinemia we found that only serum Tg levels had significantly positive correlation while other components had slightly positive correlation and levels of HDL had slightly negative correlation.

Positive correlation between serum Tg and Hcy levels that we found in the current study is in correlation with results of other authors [29] and could be explained by inhibition of fatty acid oxidation caused by Hcy which leads to serum Tg elevation [30]. Some in vitro experiments on human cells showed that Hcy induce endoplasmic reticulum stress which leads to higher expression of genes responsible for cholesterol and Tg biosynthesis, as well as their takeover and accumulation in cells [31].

We did not find a positive correlation between visceral obesity, measured by WC, and plasma homocysteine level. Conflicting data have been published on the association of Hcy and obesity. Most studies showed that body mass index (BMI), as a measure of obesity, did not correlate with Hcy level. On the other hand, abdominal adiposity was significant

predictor of plasma Hcy level [32,33]. Recent meta-analysis by Wang et al. showed that homocysteine concentrations were significantly elevated among obese patients [34]. These are in contradiction to findings of this study.

Conclusion

In conclusion, we can say that patients with IS had high prevalence of MetS and HHcy as significant risk factors for this disease. MetS and Hcy interact in promotion of atherosclerotic vascular diseases such as IS but nature of this association is not fully clear and understood. This was a cross-sectional study and we did not follow changes of plasma Hcy level in post-stroke period. Some studies showed that elevated Hcy during the convalescent phase of acute stroke was independently associated with an increased risk of recurrent ischemic stroke, especially in those patients with large-vessel atherosclerosis ischemia [35]. Further studies are needed to clarify the pathogenetic link between HHcy and MetS in stroke, as well as dynamic of plasma Hcy level in stroke and post-stroke period.

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Ethical approval. The Ethics Committee of the Institute for Physical Medicine and Rehabilitation "Dr Miroslav Zotović", Banja Luka, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Povezanost metaboličkog sindroma i homocisteinemije kod ishemijskog moždanog udara

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Uvod. Moždani udar predstavlja jedan od vodećih uzroka morbiditeta i mortaliteta širom svijeta. Povezanost između metaboličkog sindroma (MetS) i homocisteinemije (Hcy) kao faktora rizika za ishemijski moždani udar (IMU) nije dovoljno rasvijetljena. Cilj istraživanja je bio da se ustanovi učestalost MetS, nivo Hcy u serumu i učestalost hiperhomocisteinemije (HHcy), kao i njihova međusobna povezanost kod oboljelih od IMU.

Metode. Istraživanjem su bila obuhvaćena 53 ispitanika na rehabilitaciji nakon IMU i 40 ispitanika kontrolne grupe koji su bili na rehabilitaciji zbog bola u leđima starosti od 50 do 70 godina. Dijagnoza IMU je postavljena uvidom u medicinsku dokumentaciju i svi bolesnici su morali imati dijagnozu potvrđenu „imaging" metodom (KT ili MR endokranijuma). Svim ispitanicima kontrolne grupe isključeno je postojanje ranijih moždanih i srčanih udara, angine pektoris i periferne vaskularne bolesti. Dijagnoza MetS je postavljena na osnovu usaglašenih, zajedničkih kriterijuma iz 2009. godine.

Rezultati. Učestalost MetS je bila značajno viša kod bolesnika sa moždanim udarom u odnosu na kontrolnu grupu (88,7% vs. 70,0%, $p<0,05$). Nivo Hcy u serumu i učestalost HHcy su bili viši kod bolesnika sa moždanim udarom u odnosu na kontrolnu grupu (15,0±5,50 µmol/L vs. 11,2±2,51 µmol/L, $p<0,01$ i 39,2% vs. 11,4%, $p<0,01$). Pacijenti sa IMU i MetS imali su veću učestalost HHcy u odnosu na one bez MetS (42,2% vs. 16,7%, $p<0,05$) i njena učestalost je rasla sa porastom broja pojedinačnih komponenti sindroma (11,1% kod pacijenata sa 3 komponente, 36,8% kod pacijenata sa 4 komponente i 64,7% kod pacijeneta sa 5 komponenti, $p<0,05$). Nivo Hcy u serumu je bio u pozitivnoj korelaciji sa nivoom triglicerida u serumu.

Zaključak. Naši rezultati sugerišu da MetS i Hcy predstavljaju značajne faktore rizika za nastanak IMU. Čini se da postoji povezanost između ovih faktora rizika u patogenezi IMU, ali su potrebna daljnja istraživanja da bi se potvrdila ova hipoteza.

Ključne riječi: ishemijski moždani udar, metabolički sindrom, homocistein, ateroskleroza, gojaznost