ACCEPTED MANUSCRIPT

Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the Vojnosanitetski Pregled. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article: THE CORRELATION BETWEEN METABOLIC SYNDROME QUANTIFICATION SCORES AND NUMEROUS LABORATORY PARAMETERS RELATED TO THIS SYNDROME

Na srpskom

Authors Branko Srecković1, Igor Mrdović2,10, Ivan Soldatović3,10, Mirko Resan4, Nenad Janeski5, Emina Ćolak6, Hristina Janeski7, Mirjana Šumarac-Dumanović9,10, Miloš Joković8,10, Nebojša Ivanović1,10, Jasna Gačić1,10, Vesna Dimitrijević-Srecković9,10 Vojnosanitetski pregled (2018); Online First September, 2018.

UDC:

DOI: https://doi.org/10.2298/VSP180626132S

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
THE CORRELATION BETWEEN METABOLIC SYNDROME QUANTIFICATION SCORES AND NUMEROUS LABORATORY PARAMETERS RELATED TO THIS SYNDROME

Branko Srecković1, Igor Mrdović2,10, Ivan Soldatović3,10, Mirko Resan4, Nenad Janeski5, Emina Čolak6, Hristina Janeski7, Mirjana Šumarac-Dumanović9,10, Miloš Joković8,10, Nebojša Ivanović1,10, Jasna Gačić1,10, Vesna Dimitrijević-Srecković9,10

1Clinical Center "Bežanijska kosa", Belgrade, Serbia; 2Emergency Center, 3Clinic for Cardiovascular Diseases, Belgrade Serbia; University of Belgrade, Faculty of Medicine, 4Institute for Medical Statistics and Informatics, Belgrade, Serbia; 5Military Medical Academy, Belgrade, Serbia; 6Clinical Center Zemun, Belgrade, Serbia; Clinical Center of Serbia, 7Institute of Medical Bichemistry, 8University Children’s Hospital, 9Clinic for Neurosurgery, 10Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia; University of Belgrade, 10Faculty of Medicine, Belgrade, Serbia

Corresponding author
Branko Srećković, Krupanjska 24
11000 Belgrade, Serbia
Abstract

**Background / Aim.** Metabolic syndrome (MS) is characterized by basic cluster risk factors (waist circumference (WC), glucoregulation disorders, hypertension, hypertriglyceridemia, low HDL-cholesterol followed by co-founding factors such as insulin resistance (IR), C-reactive protein (CRP), uric acid, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, hyperhomocysteinemia (HHcy), non alcoholic fatty liver disease (NAFLD) and microalbuminuria. This study analyzed basic and co-founding factors of MS in patients with and without MS. Also, we analyzed correlation of siMS score, siMS risk score with basic and co-founding factors of MS. Methods. The present study included 148 overweight (body mass index (BMI) 25-30 kg/m²) and obese patients (BMI>30kg/m²) age 30–75 years, classified into two groups: I-with MS (68 patients); II-without MS (80 patients). siMS score, as a method for quantification of MS, and siMS risk score, as atherosclerotic complications risk indicator was used. Results. Patients with MS had statistically higher values of WC, hypertension, triglycerides (P<0.001), glycemia (p=0.006), so as values of co-founding factors of MS (homeostatic model assessment (HOMA-IR) (p=0.002), CRP (p=0.01), uric acid (p<0.001), alanin transaminase (ALT) (p=0.007) and gamma-glutamyl transferase (GGT) (p=0.001) and lower values of HDL-cholesterol (p<0.001) compared with patients without MS. siMS score has shown correlation with co-founding factors of MS (log HOMA IR, logCRP, uric acid, (p<0.001), fibrinogen (p=0.005), liver enzymes logALT (p=0.001) and log GGT (p<0.001) and renal parameters (creatinine (p=0.013) and serum protein (p=0.006)). siMS risk score correlates significantly with homocysteine, platelets, uric acid, blood urea nitrogen (BUN), albumins and proteins. Conclusion. In our study we found that patients with MS had higher values of co-founding factors of MS (HOMA-IR, CRP, uric acid, ALT, GGT), this is confirmed by correlation with siMS score. siMS score further indicates that IR, CRP, fibrinogen, uric acid and NAFLD are co-founding factors of MS. siMS risk score is another score that indicates that obesity and hyperprotein diet aggravates hyperhomocysteinemia with age, increasing the risk for renal dysfunction and promoting atherosclerotic complications.

**Keywords:** homocysteine, metabolic syndrome, siMS score, siMS risk score, non-alcoholic-fatty-liver disease.

Apstrakt

**Uvod / Cilj.** Metabolički sindrom (MS) karakterišu osnovni faktori (obim struka (OS), poremećaji glikoregulacije, hipertenzija, hipertrigliceridemija, nizak HDL-bolestit (IR), Creaktivni protein (CRP), acidum urikum, inhibitor aktivacije plazminogena-1 (PAI-1), fibrinogen, hiperhomocisteinemija (HHci), nealkoholna-masna bolest jetre (NAMBJ) i mikroalbuminurija. Osnovne i pridružene faktore MS analizirati kod pacijenata sa i bez MS. Ispitati korelaciju siMS skora, siMS skora rizika sa osnovnim i pridruženim faktorima MS. **Metode.** Ispitanje uključuje 148 pacijenta prekomerne telesne težine (BMI 25-30kg/m²) i gojaznog (BMI>30kg/m²) starosti 30–75 godina, podeljenih u dve grupe: I-sa MS (68 pacijenata) i II-bez MS (80 pacijenata). Korišćen je siMS skor, kao metod za kvantifikaciju MS i siMS skora rizika aterosklerotskih komplikacija. **Rezultati.** Pacijenti sa MS imali su statistički značajno više vrednosti OS, hipertenzije, triglicerida (p<0.001), glikemije (p=0.006) kao i pridruženih faktora MS.
(HOMA IR (p=0.002) CRP (p=0.01) mokraćne kiseline (p<0.001), jetrinih parametara ALT (p=0.007) i GGT (p=0.001) i niže vrednosti HDL-cholesterola, (p<0.001) u odnosu na pacijente bez MS. siMS skor je pokazao korelaciju sa pridruženim faktorima MS (log HOMA IR, logCRP, mokraćnom kiselinom, (p<0.001) i fibrinogenom (p=0.005) jetrini parametrima logALT, (p=0.001), log GGT, (p<0.001) i bubreznim parametrima (kreatininom (p=0.013) i serumskim proteinima (p=0.006). siMS skor rizika statistički značajno korelirao je sa homocisteinom, trombocitima, mokraćnom kiselinom, ureom, albuminima i proteinima.

Zaključak. Statistički značajno više vrednosti pridruženih faktora MS (HOMA-R, CRP, mokraćne kiseline, ALT, GGT) kod pacijenata sa MS potvrđene su i korelacijom sa siMS skorom. siMS skor ukazuje da su IR, CRP, fibrinogen, mokraćna kiselina, NAMBJ pridruženi faktori MS. siMS skor rizika ukazuje da gojaznost i hiperproteininski unos povećavaju hiperhomocisteinemiju sa starenjem, rizik bubrežnih poremećaja i aterosklerotskih komplikacija.

Ključne reči: homocistein, metabolički sindrom, siMS skor, siMS skor rizika, ne-alkoholna masna bolest jetre (NAMBJ)

Introduction

Hyperhomocysteinemia (HHcy) was found in some age-related clinical entities such as osteoporosis, hypothyroidism, cardiovascular diseases (CVD), cancer, end renal stage disease and neurodegenarative diseases. Hcy is increased by sveral mechanisms as methionine enriched diets, defects in the methionine metablism and B6, B12 and folate deficits. Homocysteine directly correlated well with age, waist circumference, fasting glucose, triglyceride, uric acid, fibrinogen levels, insulin resistance, and inversely with creatinine clearance, and HDL-cholesterol. Animal studies suggested HHcy as additional component of the MS. Studies were based on theory that insulin might affect homocysteine metabolism, in which hyperinsulinism caused increased levels of homocysteine. Further studies have shown that MS and HHcy are established independent risk factors for cardiovascular diseases, and HHcy might be co-founding factor of MS.

In our previous studies correlation of siMS score with Hcy indicated that Hcy is a co-founding factor of MS. siMS score defined by I. Soldatoivc et al. presents summary score of all MS factors (abdominal obesity, glycaemia, systolic and diastolic pressure, triglycerides and HDL-cholesterol). siMS score correlates with uric acid, microalbuminuria, fibrinogen, as well as with inflammation parameter C- reactive protein (CRP). Next clinical entity, non-alcoholic fatty liver disease (NAFLD) is also considered as a sign of MS. NAFLD is a chronic liver disease, which includes a spectrum of hepatic pathology from simple steatosis, steatohepatitis, to cirrhosis. Inresed Hcy may be associated with hepatic fat accumulation, both caused by hyperinsulinism. Hcy induces endothelial cell injury and impairs vasodilatation by increased inactivation of nitric oxide and decreased generation of nitric oxide. Homocysteine promote oxidative stress in vascular cells and tissues by reactive oxygen species (ROS), who have been shown to cause endothelial injury and the development of atherosclerosis. Correlation between Hcy, hypertension and hyperlipoproteinemia indicated that Hcy could be promoting factor for atherosclerosis.
Aim of this study was to analyze and correlate MS cluster factors (waist circumference, glycoregulation disorders, hypertension, hypertrigliceridemia, low HDL-cholesterol) and co-founding factors of MS (insulin resistance, CRP, urica acid, plasminogen activator inhibitor-1, fibrinogen, hyperhomnocysteinemia, NAFLD and microalbuminuria) in patients with MS and without MS. siMS score and siMS risk score correlation with basic cluster MS factors and co-founding factors was examined.

Methods

The present study included 148 overweight (BMI 25-30 kg/m²) and obese (BMI>30kg/m²) patients aged 30–75 years classified into two groups: I- with MS (68 patients); II- without MS (80 patients). Measured anthropometric parameters were body weight, body height body mass index, waist circumference. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of body height in meters. Blood pressure was measured in seating position using sphygmomanometer. Oral glucose tolerance test (OGTT) with 75 gr glucose was used for estimation of glycoregulation early disorders. Values of glycaemia and insulin were measured during OGTT in 0, 30 and 120 minutes. Lipid status was determined by total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides by spectrophotometer methods and Apo A1, Apo B, Apo E and Lp(a) by immunochemical methods. ATP III classification was applied for diagnosing MS. A diagnosis of MS is confirmed if three out of five parameters are found as follows: waist circumference (WC >102 cm for males and >88 cm for females), blood pressure (BP > 135/85 mm/Hg), fasting blood glucose (>6.1 mmol/L), increased triglycerides (>1.7 mmol/L), decreased HDL-C (< 1.03 mmol/L for males and HDL-C < 1.29 mmol/L for females). Patients who consumed more than 2 units of alcohol (for females) per day, or 3 units per day (for males), or more than 14 units per week (females) and 21 units per week (for males) respectively, were excluded from the study. (One unit of alcohol (10g) is equivalent to one glass of whiskey-3cl, or one glass of brandy-3cl, or one glass of wine-20cl, or one glass of beer-25cl).

In this study we analyzed cluster factors of MS and co-founding factors such as insulin resistance, homocysteine, C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), fibrinogen, urica acid, liver and renal function parameters. Insulin was measured using the radioimmunoassay method. Insulin resistance and insulin sensitivity was determined by HOMA IR. Homocysteine as an independent marker of atherosclerosis was determined on Abbott’s Architect analyzer, using CMIA technology. Levels of CRP as an inflammation marker were determined by immunometric method. PAI-1 as an thrombogenic marker was determined by plasminogen substrate essay. Liver function parameters determined were aspartate aminotransferase (AST), alanine aminotransferase (ALT), g-glutamyl-transpeptidase (GGT), albumin, total proteins. Renal function parameters determined were urea, creatinine, creatinine clearance, microalbuminuria from 24-hour urine, by immune-nephelometric method. Soldatovic I. established a new siMS score for metabolic syndrome quantification, simple for clinical use and scientific research.
The formula for siMS score using MS reference values is calculated as follows:

\[
\text{siMS score} = \frac{2 \times \text{Waist}}{\text{Height}} + \frac{\text{Glycemia}}{5.6} + \frac{\text{Tg}}{1.7} + \frac{\text{TA systolic}}{130} - \frac{1.03 \text{ or } 1.3 (\text{male or female})}{1.03 \text{ or } 1.3 (\text{male or female})}
\]

Age and positive family anamnesis were added to siMS score; siMS risk score, useful for cardio/cerebrovascular events risk evaluation, was thus obtained. 

\[
\text{siMS risk score} = \text{siMS score} \times \left( \frac{\text{Age}}{45 \text{ or } 50 (\text{males or females})} \right) \times \left( \frac{\text{Family history of cardio or cerebrovascular event}}{\text{event} = 1.2, \text{else} = 1} \right)
\]

Complete internist-cardiology examination: ECG, blood pressure and other methods necessary or possible to determine the cardiac status were carried out.

**Ethics**

The Ethical Committee of Medical Faculty, Belgrade University approved the present study. All patients have given their consent.

**Statistics**

Data are presented as count (%) or mean±standard deviation, depending on data type. Student's T test and Mann-Whitney U test were used to assess significant differences between groups. Pearson correlation was used to explore the significant relationship between HCY and other parameters. All p values less than 0.05 were considered significant. All data were analyzed using SPSS 20.0 (IBM corp.) statistical software.

**Results**

The present study included 148 overweight and obese patients, age 30–75 years, BMI>25 kg/m², classified into two groups: I- with MS (68 patients); II- without MS (80 patients). Average age of patients with MS was 46.69±15.04 years, while average age of patients without MS was 47.73±16.66 years (p>0.5). MS was found in 45.95% of patients. The gender distribution was as follows: in the MS group, there was 20.3% of male and 79.7% of female patients, while in the group of MS free patients, there was 5.6% of male and 94.4% of female patients.

Anthropometric parameters (body weight, BMI, WC, systolic blood pressure, diastolic blood pressure, mean blood pressure (p<0.001)) were statistically much higher in patients with MS than in patients without MS. Higher fasting glycaemia (p=0.006) and significantly higher values of triglycerides (p<0.001) as well as lower HDL-cholesterol (p<0.001) were also found in patients with MS. (Table 1). The distribution of patients regarding to each criterion, showed that the increased waist circumference had 88.0% of patients, 48.2% of patients had hypertension, 21.2% of patients had hyperglycemia, 45.9% of patients had increased triglyceride values and 38.1% of patients had decreased HDL-cholesterol.
Table 1.
Anthropometrical and biochemical MS parameters in patients with MS and without MS

<table>
<thead>
<tr>
<th></th>
<th>With MS</th>
<th>Without MS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.7±15.0</td>
<td>47.7±16.7</td>
<td>0.695</td>
</tr>
<tr>
<td>Gender male</td>
<td>21 (30.9%)</td>
<td>15 (18.8%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>13 (20.3%)</td>
<td>4 (5.6%)</td>
<td>0.009</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>97.3±20.1</td>
<td>82.7±17.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.2±6.1</td>
<td>29.5±6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>105.8±14.4</td>
<td>92.7±14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>s BP (mmHg)</td>
<td>135.8±12.1</td>
<td>118.7±11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>d BP (mmHg)</td>
<td>88.1±8.8</td>
<td>77.8±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP mean (mmHg)</td>
<td>104.0±8.9</td>
<td>91.4±9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.9±1.2</td>
<td>5.8±1.2</td>
<td>0.669</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.22±0.3</td>
<td>1.45±0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.65±1.2</td>
<td>3.7±1.1</td>
<td>0.627</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.1±0.9</td>
<td>1.3±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycaemia (mmol/l)</td>
<td>5.4±1.4</td>
<td>4.9±0.8</td>
<td>0.006</td>
</tr>
</tbody>
</table>

The results are expressed as mean value ± SD

Insulin values (p=0.007), insulin at 120 minute during OGTT (p=0.014), mean value insulin in OGTT (P=0.066) and HOMA-IR (p=0.002) were significantly higher in patients with MS. Higher Apo B (p=0.01), CRP (p=0.01), uric acid (p<0.001) and liver enzymes ALT (p=0.007) and GGT (p<0.001) were also found in patients with MS. Thrombocytes, fibrinogen, PAI-1, urea, creatinine, creatinine clearance, microalbuminuria values were higher in patients with MS than in those without MS but without any significance (p>0.5). (Table 2.)

In order to determine the effect of MS on liver enzymes, a dual factorial analysis of variance was used, in which MS and alcohol consumption were independent variable, and ALT and GGT were dependent variables. Based on this analysis, it was found that MS correlates with ALT and GGT independent of alcohol consumption (p = 0.011; p <0.001).
Table 2. Metabolic syndrome co-founding parameters in patients with MS and without MS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>With MS</th>
<th>Without MS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>13.3±3.6</td>
<td>12.9±4.2</td>
<td>p=0.119</td>
</tr>
<tr>
<td>Insulin fasting (mU/l)</td>
<td>31.2±31.5</td>
<td>20.9±16.8</td>
<td>p=0.007</td>
</tr>
<tr>
<td>Insulin at 120 minute (mlU/l)</td>
<td>61.6±42.3</td>
<td>45.8±45.4</td>
<td>p=0.014</td>
</tr>
<tr>
<td>Mean value insulin (mU/l)</td>
<td>63.0±52.8</td>
<td>52.8±36.8</td>
<td>p=0.066</td>
</tr>
<tr>
<td>HOMA IR (µmol/mU/ml)</td>
<td>7.7±8-6</td>
<td>4.5±3.7</td>
<td>p=0.002</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>5.5±6.8</td>
<td>3.7±5.4</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Uric acid (µmol/l)</td>
<td>359.2±85-6</td>
<td>307.3±77.9</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Thrombocytes (10^9/L)</td>
<td>268.5±62.8</td>
<td>253.4±63.1</td>
<td>p=0.153</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.8±0-8</td>
<td>3.7±0-7</td>
<td>p=0.517</td>
</tr>
<tr>
<td>PAI-1 (U/ml)</td>
<td>5.98±1.84</td>
<td>5.77±1.78</td>
<td>p=0.776</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>25.2±15.2</td>
<td>22.9±7.6</td>
<td>p=0.227</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>29.7±20.3</td>
<td>23.0±11.8</td>
<td>p=0.007</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>28.7±14.8</td>
<td>19.5±11.9</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>4.9±1.3</td>
<td>4.7±1.1</td>
<td>p=0.467</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>76.9±15.8</td>
<td>72.9±15.1</td>
<td>p=0.115</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>121.7±57.3</td>
<td>111.4±33.4</td>
<td>p=0.224</td>
</tr>
<tr>
<td>Microalbuminuria (mg/24h)</td>
<td>81.9±80.8</td>
<td>55.9±57.4</td>
<td>p=0.225</td>
</tr>
<tr>
<td>ApoA1 (g/l)</td>
<td>1.64±0.38</td>
<td>1.61±0.27</td>
<td>p=0.603</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>1.12±0.28</td>
<td>0.96±0.26</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Apo A2 (g/l)</td>
<td>357.9±65.5</td>
<td>351.0±66.6</td>
<td>p=0.674</td>
</tr>
<tr>
<td>Apo E (g/l)</td>
<td>47.0±12.3</td>
<td>43.3±14.5</td>
<td>p=0.255</td>
</tr>
<tr>
<td>Lp (a) (g/l)</td>
<td>0.166±0.185</td>
<td>0.236±0.290</td>
<td>p=0.223</td>
</tr>
</tbody>
</table>

The results are expressed as mean value ± SD

Presence of MS factors in patients with MS was as follows: 6.9% patients with no MS factors, 17.2% with one MS factor, 31% with two MS factors, 26.9% with three MS factors, 15.2% with four MS factors and 2.8% with all five MS factors. (Figure 1.)
Fig. 1 – Percent of patients with metabolic syndrome components

Homocysteine correlated significantly (Pearson’s correlation) with thrombocytes (p=0.046), urea (p=0.002), creatinine (p=0.006), creatinine clearance (p=0.047) and siMS risk score (p=0.015).

The siMS score confirmed significant correlation with log CRP, uric acid, log HOMA IR, log GGT (p<.001), log ALT (p=0.001), thrombocytes (p=0.01), fibrinogen (p=0.005), proteins (p=0.006), creatinine (p=0.013). This risk score showed a statistically significant correlation with urea (p<0.01), albumin (p=0.003), total proteins (p=0.057), thrombocytes (p=0.046), uric acid (p=0.038), homocysteine (0.015). (Table 3).

Table 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>siMS score</th>
<th>siMS risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
<td>0.120 (0.177)</td>
<td>0.215 (0.015)</td>
</tr>
<tr>
<td>Log HOMA IR</td>
<td>0.457 (&lt;0.001)</td>
<td>0.130 (0.181)</td>
</tr>
<tr>
<td>Log CRP</td>
<td>0.333 (&lt;0.001)</td>
<td>-0.125 (0.189)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.336 (&lt;0.001)</td>
<td>0.183 (0.038)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.250 (0.005)</td>
<td>-0.099 (0.272)</td>
</tr>
<tr>
<td>Thrombocytes</td>
<td>0.281 (0.001)</td>
<td>-0.176 (0.046)</td>
</tr>
<tr>
<td>Log ALT</td>
<td>0.281 (0.001)</td>
<td>0.105 (0.237)</td>
</tr>
<tr>
<td>Log GGT</td>
<td>0.369 (&lt;0.001)</td>
<td>0.114 (0.211)</td>
</tr>
<tr>
<td>Total proteins</td>
<td>0.241 (0.006)</td>
<td>-0.168 (0.057)</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.037 (0.681)</td>
<td>-0.265 (0.003)</td>
</tr>
<tr>
<td>Urea</td>
<td>0.040 (0.649)</td>
<td>0.388 (&lt;0.001)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.218 (0.013)</td>
<td>-0.115 (0.191)</td>
</tr>
</tbody>
</table>

*Results are presented as correlation coefficient and p value (in brackets)

The Figure 2 showed the correlation between siMS score and log HOMA IR, log CRP, fibrinogen, log ALT, log GGT, and correlation between siMS risk score with homocysteine
Fig. 2 – The correlation between siMS score and log HOMA IR, log CRP, fibrinogen, log ALT, log GGT and the correlation between siMS risk score and homocysteine

Discussion

Chronic diseases as diabetes, osteoporosis, hypothyroidism, so as renal dysfunction, so as diet are considered to be associated with moderately elevated homocysteine concentrations\(^a\). Homocysteine is amino acid formed in metabolism cycle of methionine to cysteine. Hyperhomocysteinemia, is recognized as an independent risk factor for atherosclerosis\(^b\). Connection of Hcy and insulin resistance is explained by disruption of insulin signaling by Hcy interfering phosphorylation of insulin receptors. Result of this impaired insulin receptor signal cascade is in lowered GLUT4 translocation to the plasma membrane and therefore reduced glucose uptake\(^c\). Catena et al. showed that plasma Hcy was directly correlated with age, factor of MS and insulin resistance, while inversely correlated with creatinine clearance and high-density lipoprotein cholesterol, vitamin B12, and folate levels\(^d\). A correlation of homocysteine with hypertension and hyperlipoproteinemia in our previous studies indicates that homocysteine can be an important indicator of risk for atherosclerotic complications and progression of these\(^e\). Sheu et al. found in their studies higher homocysteine values in hypertensive patients than in normotensive ones, significant correlation of plasma Hcy with insulin values in OGTT was also found\(^f\). The latest results of our studies showed a positive correlation of homocysteine with long term glucoregulation parameter HbA1C, HOMA-IR, Apo B, and negative correlation with Apo E. The siMS score significantly correlated with homocysteine, uric acid, microalbuminuria, thrombosis factor-fibrinogen, inflammation factor-CRP, and confirmed that these are metabolic syndrome co-founding factors. Our study in patients with coronary heart disease have shown correlation between Hcy and the systolic pressure, triglycerides and uric acid, which confirms association of Hcy with insulin resistance and MS as well as the further risk of atherosclerosis complications\(^g\).

Patients with MS covered by the present study were characterized by statistically important much higher values of anthropometric parameters (body weight, BMI, waist
circumference), blood pressure, triglycerides, insulinemia in OGTT 0’ and 120’, mean value insulin, HOMA-IR, CRP, uric acid, Apo B as well as liver function parameters ALT and gamma GT which are markers of NAFLD and statistically lower HDL-C. Summarized above mentioned this results indicate that patients with MS had higher values of basic cluster factors of MS (waist circumference, hypertension, hyperlipoproteinemia type IV) so as values of co-founding factors of MS such as hyperinsulinemia, insulin resistance, CRP, uric acid and NAFLD. Abdominal obesity and IR have a significant role in MS development. Recent studies have shown that patients with MS had significantly higher levels of high sensitive CRP, compared to control group, which is a marker of chronic inflammation in patients with MS, whose values increased linearly with the increase number of factors for MS. Obesity is characterized by elevated inflammatory factors such as CRP and prothrombogenic factors such as fibrinogen, which occur before other MS disorders and are useful in the assessment of cardiovascular risk.

Results obtained by Dimitrijevic-Sreckovic et al. indicate the existence of NAFLD even in the youngest obese population: children 7.3%, adolescents 18.9%, and youth 20 to 30 years old 29%. NAFLD is a liver sign of MS, while youth with NAFLD manifested, besides increased ALT and gamma GT values, abdominal obesity, hyperinsulinemia in OGTT, pronounced insulin resistance, increased triglycerides, CRP and uric acid. The study of Colak and associates have also shown elevated liver enzymes in obese students with increased risk for cardiovascular disease. Other studies of obese and adolescent population indicate the association of NAFLD with insulin resistance.

The siMS score showed in the present study a correlation with MS co-founding factors (log CRP, uric acid, log HOMA-IR, fibrinogen, platelets), liver parameters (log ALT, log GGT) and hyperproteinemia, retention of nitrogen substances and increased risk for kidney damage. The correlation of siMS score with liver function parameters indicates that fatty liver is a MS co-founding factor. Homocysteine is an intermediate in methionine metabolism, which takes place mainly in the liver. Result of impaired remethylation of homocysteine to methionine leads to increased levels of homocysteine promoting the liver damage from NAFLD to non alcoholic steatohepatitis.

Correlation of siMS score with renal function parameters creatinine and total proteins as shown in the present study indicates that even initial renal function disorders can represent MS co-founding factors. Higher values of microalbuminuria in patients with MS compared to patients without MS indicate the initial stage of kidney damage in obese patients. Our previous studies have shown the appearance of microalbuminuria in obese children, adolescents and young people, which are normalized after weight reduction. Correlation of homocysteine with platelets, renal function parameters (urea, creatinine, creatinine clearance) and siMS risk score was also confirmed. Hyper-protein diet based on meat and dairy products, most frequent in MS obese people nutrition, can contribute to increased glomerular filtration with increased creatinine clearance and provoke hyperhomocysteinemia and renal damage. Berstad et al. have shown that higher intake of animal saturated fatty acids correlated positively with higher homocysteine levels. Microalbuminuria as co-founding factor of MS is a strong indicator of cardiovascular disease and renal dysfunction. It is suggested that HHcy enhances oxidative stress, inducing endothelial and mesangial cell dysfunction, resulting in microalbuminuria. High animal-protein diet correlates positively with high Hcy levels, whereas high plant-protein diet inversely correlates with total Hcy levels. A correlation of siMS score with liver and renal function parameters indicates that disorders of these systems could appear in obese
patients as co-founding MS factors. Hyperhomocysteinemia can be caused by increased intake of proteins from dairy and meat products abounding in saturated fats of animal origin and reduced intake of vegetables rich in folic acid, which all contributes to progression of atherosclerotic complications, fatty liver and renal damage.

The siMS risk score of the present study correlated with homocysteine, platelets, uric acid and renal function parameters (urea, total albumins and proteins). These results indicate that hyperhomocysteinemia increases with age and represents a vascular complications risk indicator. Correlation with uric acid indicates that obesity with its co-founding factors contributes considerably to vascular complications and values of total proteins and albumins which increase as a result of hyperproteic intake.

Mediterranean diet rich in dietary fibers and complex carbohydrates in fruits, vegetables and cereals, monounsaturated fats in olive oil, omega-3 polyunsaturated fats in fish and reduction of saturated fats and proteins of animal origin proved favorable effects on body mass reduction, glucose regulation, hypertension, lipid status, insulin resistance, inflammatory and thrombotic factors, and HHcy. Han et al. highlight the importance of increasing folic acid and vitamin B supplementation, or by diet which consists of daily fruit and vegetable intake, healthy lifestyle based on regular exercise and refraining from tobacco smoking and alcohol consumption for prevention of HHcy.

In conclusion patients with MS had statistically significant higher values of co-founding factors of MS (HOMA-IR, CRP, uric acid, ALT, GGT) which correlated well with siMS score. siMS score correlation with fibrinogen, creatinine and proteins indicates that thrombosis factors so as renal function parameters could be co-founding factors of MS. Used as a method of quantification of MS, siMS score confirms that abdominal obesity followed by hyperinsulinism and insulin resistance promotes the risk for glucose regulation disorders (prediabetes and diabetes type 2), hyperlipoproteinemia type IV (elevated triglycerides and low HDL-C), hypertension so as for co-founding factors of inflammation (CRP), thrombosis (fibrinogen), elevated ALT i GGT as a sign of NAFLD, uric acid, microalbuminuria and nitrogen retention as a sign of renal dysfunction.

siMS risk score correlation with homocysteine, platelets, uric acid and parameters of renal function (urea, proteins and albumins) indicates that some co-founding factors of MS aggravates with age and hyper-protein diet which elevates homocysteine levels contribute further to retention of nitrogen products and promotes renal dysfunction so as atherosclerotic complications.

REFERENCES:


8. De Carvalho SC, Muniz MT, Siqueira MD, Siqueira ER, Gomes AV, Silva KA, Bezerra LC, D Almeida V, de Oliveira CP, Pereira LM. Plasmatic higher levels of homocysteine in non-alcoholic fatty liver disease (NAFLD) Nutr J 2013 Apr 2, 12:37


Received on June 26, 2018
Revised on August 17, 2018
Accepted on September 3, 2018
Online first September 2018

Abbreviations:

MS-Metabolic syndrome
IR-insulin resistance
NAFLD-non-alcoholic-fatty liver disease
Hcy-homocysteine
HHcy-Hyperhomocysteinemia
ROS-reactive oxygen species
CVD- cardiovascular disease
CIMT-carotid intima-media thickness
WC-waist circumference
BMI-body mass index
OGTT-oral glucose tolerance test
HOMA IR-Homa insulin resistance index
AST-aspartate aminotransferase
ALT-alanine aminotransferase
GGT-g-glutamyl-transpeptidase
CRP-C reactive protein
BP-blood pressure
ACC-arteria carotis communis
ACI-arteria carotis interna
ACE-arteria carotis externa
AFS-superficial femoral arteries
Met-methionine
Cys-cysteine
ER stress-endoplasmic reticulum stress
Author's e-mail addresses:

Mr sci med dr Branko Srečković e-mail: drsreckovic65@gmail.com tel.0692667721
Prof dr Igor Mrdović, e-mail: igormrd@gmail.com tel. 063462488

Doc dr Ivan Soldatović, e-mail: soldatovic.ivan@gmail.com tel. 0642305319

Doc dr Mirko Resan, e-mail: resan.mirko@gmail.com tel 062372159

Dr Nenad Janeski, e-mail: drjaneski@gmail.com tel 0616235800

Primarius Dr sci Emina Čolak, e-mail: emina.colak.bg@gmail.com tel.0641250162

Dr Hristina Janeski, e-mail: opethristina@gmail.com tel. 0605454205

Prof dr Mirjana Šumarac-Dumanović, e-mail: msumaracdumanovic@gmail.com
tel.0637766522

Prof dr Miloš Joković, e-mail: severovo@yahoo.com tel. 0646231819

Prof dr Nebojša Ivanović, e-mail: ivanovicnebojsadr@gmail.com tel.0603947871

Ass dr Jasna Gačić, e-mail: jasna.gacic37@gmail.com tel.063303111

Prof dr Vesna Dimitrijević Srećković, e-mail: vesnadsendo@gmail.com tel .
0638765330