Is the combined use of insulin resistance indices, including adipokines, more reliable in metabolic syndrome?

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1. Introduction

Metabolic syndrome (MetS) is a clustering of cardiovascular risk factors associated with insulin resistance, central adiposity, hyperglycemia, hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C) levels (1,2).

Adipokines are secreted by adipose tissue and influence a variety of physiological processes such as food intake control, energy homeostasis, insulin sensitivity, angiogenesis, blood pressure regulation, and blood coagulation (3). They play significant roles in the pathogenesis of obesity, MetS, and chronic inflammatory and autoimmune diseases (4). Leptin is one adipokine that contributes to the regulation of body weight, modulation of insulin sensitivity, metabolism, and reproductive function (5). In addition, it affects thermogenesis, hematopoiesis, angiogenesis, and immune homeostasis (6). Another adipokine, adiponectin, produced exclusively by adipocytes of white adipose tissue, plays a significant role in the regulation of insulin sensitivity and has antiatherosclerotic and antiinflammatory properties (3). Resistin is another adipokine that may be involved in sensing the nutritional status—its mRNA level decreases during fasting and increases after food consumption. It is associated with a variety of disorders: obesity, diabetes, atherosclerosis, endothelial dysfunction, thrombosis, angiogenesis, inflammation, and smooth muscle cell dysfunction (4,7). The adipokine visfatin shows insulin-like properties, inhibits glucose release by liver cells, and promotes the storage of triglycerides in preadipocytes (8). It plays roles in immunity, metabolism, aging and

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inflammation, and stress response, and it participates in cardio-cerebrovascular diseases (9).

The current study had the following goals: 1) to determine the levels of leptin, resistin, adiponectin, and visfatin; 2) to investigate whether the ratios of the adipokines and of the MetS criteria give more reliable results; 3) to determine the insulin resistance and sensitivity indices; and 4) to examine the relationships among all the parameters (single and combined parameters) in MetS. This is a complicated study of adipokines, adipokine ratios, criteria ratios, and insulin resistance indices, leading to the suggestion of novel criteria.

2. Materials and methods

2.1. Study population

The study was carried out in the Departments of Medical Biochemistry and Internal Medicine of the Faculty of Medicine, Karadeniz Technical University. All participants gave informed consent and the study protocol was approved by the Local Ethics Board of the Faculty of Medicine (No. 2006/25).

The subjects were considered to have MetS if they had any 3 or more of the following criteria [according to the National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III]: 1) abdominal obesity: waist circumference (WC) of >102 cm in men and >88 cm in women; 2) hypertriglyceridemia: serum triglyceride (TG) level ≥150 mg/dL (1.69 mmol/L) and 3) low HDL-C of <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women; 4) high blood pressure: systolic blood pressure (SBP) of ≥130 mmHg and/or diastolic blood pressure (DBP) of ≥85 mmHg or receiving treatment for hypertension; and 5) high fasting blood glucose: serum glucose level of ≥110 mg/dL (6.1 mmol/L) or receiving treatment for diabetes (10).

WC was measured 2 times at the narrowest horizontal point between the costal margin and the iliac crests at the end of normal expiration to the nearest 0.1 cm. Measurements of SBP and DBP were made 3 times in sitting position after 15 min of rest and their mean was calculated. Before measuring the blood pressures, participants were advised to avoid caffeinated beverages and exercise for at least 30 min (11,12).

The study group included 45 patients with MetS (14 men/31 women) and 45 sex- and age-matched non-MetS healthy volunteers (14 men/31 women) who did not meet any MetS criteria. The patient group met the criteria in the following ratios: abdominal obesity 44/45 (97.7%), hypertriglyceridemia 43/45 (95.6%), low HDL-C 40/45 (88.9%), hypertension 33/45 (73.3%), and high fasting glucose 17/45 (37.8%). Nine of the MetS subjects met 5 criteria and the rest met 4 criteria. MetS patients with high glucose level (MetS-HGL) (n = 17, 5 men and 12 women) formed another group of interest in this study.

2.2. Determination of the biochemical parameters

Blood samples were collected in the morning after 10–12 h of fasting and the sera were separated following clotting by centrifugation at 3000 rpm for 10 min at 4 °C. Aliquots were then stored at –80 °C until the tests were performed.

Serum TG levels were measured by using a glycerol oxidase enzymatic method; HDL-C was measured by a cholesterol oxidase enzymatic method in supernatant following precipitation with phosphotungstic acid–MgCl₂; and fasting serum glucose was measured by using an enzymatic (glucose oxidase) colorimetric method. Measurements were performed with an autoanalyzer (Modular, Roche, Basel, Switzerland). Insulin levels were determined by the chemiluminescent immunometric method using an Immulite Insulin kit (Diagnostic Products Corporation, Diamond Diagnostics, Holliston, MA, USA). Reagents were supplied by the same manufacturer. The concentrations of leptin, adiponectin, and resistin were determined with commercial enzyme-linked immunosorbent assay (ELISA) kits (Cat. No. RD191001100R, RD191023100R, and RD191016100R, respectively, BioVendor, Heidelberg, Germany). Visfatin concentrations were determined using a commercially available ELISA kit (Cat. No. K4907-100, BioVision, Milpitas, CA, USA).

2.3. Calculation of ratios of parameters and indices of the insulin resistance/sensitivity

Homeostasis model assessment: insulin resistance index (HOMA-IR)

\[
\text{HOMA-IR} = \frac{\text{glucose (mg/dL)} \times \text{insulin (µU/mL)}}{405}
\] (13)

Homeostasis model assessment-adiponectin index (HOMA-AD)

\[
\text{HOMA-AD} = \frac{\text{Glucose (mg/dL)} \times \text{insulin (µU/mL)} / \text{adiponectin (µg/mL)}}
\] (14)

Adiponectin-resistin index (AR)

\[
\text{AR} = 1 + \log_{10} (\text{resistin (ng/mL)}) - \log_{10} (\text{adiponectin (µg/mL)})
\] (15)

Insulin resistance index (IRAR)

\[
\text{IRAR} = \log_{10} (\text{insulin (µU/mL)} \times \text{glucose (mg/dL)}) \times [1 + \log_{10} (\text{resistin (ng/mL)}/\text{adiponectin (µg/mL)})]
\] (15)

Mean arterial pressure (MAP) =

\[
\frac{2}{3 \times \text{DBP}} + \frac{1}{3} \times \text{SBP}
\] (16)

Pulse pressure (PP) = SBP − DBP

(16)
The ratios of some parameters were calculated by direct division and abbreviated as follows: triglyceride/glucose (TG/Glc), triglyceride/high-density lipoprotein cholesterol (TG/HDL-C), glucose/insulin (Glc/I), glucose/adiponectin (Glc/A), visfatin/adiponectin (V/A), adiponectin/leptin (A/L).

2.4. Statistical analysis
Data are expressed as means and standard deviations. The distributions of variables in the study groups were assessed by the Kolmogorov–Smirnov test. Statistical differences between data from the MetS and the control groups and between subgroups were determined according to the Student t-test (parametric) or Mann–Whitney U test (nonparametric). Relationships among variables were assessed by Spearman rank-order test (most of them) or by Pearson correlation coefficient. P < 0.05 were considered to be statistically significant.

3. Results
WC, SBP, DBP, glucose, TG, insulin, leptin, visfatin, MAP, PP, TG/HDL-C, TG/Glc, Glc/A, V/A, HOMA-IR, HOMA-AD, AR, and IRAR values were significantly higher, but HDL-C, Glc/I, and A/L values were significantly lower in the MetS group than those in the controls (Table 1). When compared with women, men in the MetS group had higher values of TG and TG/HDL-C, but lower values of HDL-C and V/A (P < 0.05). In addition, men in the control group had higher values of WC and insulin, but lower values of HDL-C (P < 0.05). On the other hand, men with MetS had increased values of WC, SBP, DBP, MAP, PP, TG, TG/Glc, TG/HDL-C, visfatin, V/A, and IRAR, but had decreased values of HDL-C compared with men in the control group (P < 0.05). All the parameters were significantly increased (P < 0.05) except resistin (P = 0.522) and Glc/I (P = 0.107) in women with MetS when compared with non-MetS women (Table 2).

Table 1. The values of anthropometric measurements and biochemical parameters in non-MetS control, MetS, and MetS-HGL groups.

<table>
<thead>
<tr>
<th></th>
<th>Non-MetS (n = 45)</th>
<th>MetS (n = 45)</th>
<th>MetS-HGL (n = 17)</th>
<th>P*</th>
<th>P**</th>
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<td>Age (years)</td>
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<td>WC (cm)</td>
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<td>SBP (mmHg)</td>
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<td>DBP (mmHg)</td>
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<td>TG/HDL-C</td>
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<td>Glucose (mg/dL)</td>
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<td>Insulin (µU/mL)</td>
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<td>Leptin (ng/mL)</td>
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<td>Adiponectin (µg/mL)</td>
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<td>Resistin (ng/mL)</td>
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<td>Visfatin (ng/mL)</td>
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<td>TG/Glc</td>
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<td>Glc/I</td>
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<td>Glc/A</td>
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<td>V/A</td>
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<td>A/L</td>
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<td>HOMA-IR</td>
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<td>HOMA-AD</td>
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<td>IRAR</td>
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*: P-values comparing the MetS with the non-MetS group.
**: P-values comparing the MetS-HGL with the non-MetS group
In the MetS group (n = 45), significant positive correlations were observed in insulin with MAP ($r = 0.295$, $P = 0.049$) and leptin ($r = 0.353$, $P = 0.017$), in PP with HOMA-IR ($r = 0.317$, $P = 0.034$) and HOMA-AD ($r = 0.309$, $P = 0.039$), and in V/A with AR ($r = 0.549$, $P < 0.001$) and IRAR ($r = 0.470$, $P = 0.001$). Moreover, negative correlations of A/L with insulin ($r = -0.349$, $P = 0.019$) and resistin ($r = -0.344$, $P = 0.021$), and visfatin with age ($r = -0.300$, $P = 0.046$), were also observed. In men with MetS (n = 14), insulin was positively correlated with SBP, DBP, and MAP ($r = 0.593$, $P = 0.026$; $r = 0.620$, $P = 0.018$; $r = 0.667$, $P = 0.009$, respectively), but Glc/I was negatively correlated with SBP ($r = -0.684$, $P = 0.007$), DBP ($r = -0.696$, $P = 0.006$), MAP ($r = -0.714$, $P = 0.004$),

### Table 2. The values of anthropometric measurements and biochemical parameters in men and women in the non-MetS and the MetS group.

<table>
<thead>
<tr>
<th></th>
<th>Non-MetS</th>
<th></th>
<th>MetS</th>
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<tbody>
<tr>
<td></td>
<td>Men (n = 14)</td>
<td>Women (n = 31)</td>
<td>Men (n = 14)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 ± 6</td>
<td>36 ± 6</td>
<td>39 ± 7</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>87 ± 7</td>
<td>77 ± 7</td>
<td>107 ± 7</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>113 ± 10</td>
<td>112 ± 9</td>
<td>141 ± 17</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 ± 7</td>
<td>71 ± 7</td>
<td>94 ± 14</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>87 ± 7</td>
<td>85 ± 6</td>
<td>109 ± 15</td>
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<tr>
<td>PP (mmHg)</td>
<td>38 ± 8</td>
<td>41 ± 9</td>
<td>48 ± 9</td>
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<tr>
<td>TG (mg/dL)</td>
<td>75 ± 30</td>
<td>68 ± 23</td>
<td>275 ± 128</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>60 ± 10</td>
<td>67 ± 9</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>TG/HDL-C</td>
<td>1.35 ± 0.69</td>
<td>1.05 ± 0.43</td>
<td>8.66 ± 4.76</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>83 ± 8</td>
<td>83 ± 10</td>
<td>114 ± 54</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>11.68 ± 5.23</td>
<td>8.53 ± 4.39</td>
<td>20 ± 18</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>7.68 ± 4.23</td>
<td>8.60 ± 3.75</td>
<td>12.93 ± 8.07</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>7.85 ± 3.86</td>
<td>8.55 ± 5.17</td>
<td>7.88 ± 3.58</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>7.53 ± 5.88</td>
<td>10.55 ± 6.04</td>
<td>10.87 ± 5.99</td>
</tr>
<tr>
<td>Visfatin (ng/mL)</td>
<td>29 ± 13</td>
<td>30 ± 17</td>
<td>48 ± 18c</td>
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<tr>
<td>TG/Glc</td>
<td>0.90 ± 0.35</td>
<td>0.84 ± 0.34</td>
<td>2.70 ± 1.40</td>
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<tr>
<td>Glc/I</td>
<td>10.36 ± 9.52</td>
<td>13.33 ± 8.48</td>
<td>8.56 ± 5.50</td>
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<tr>
<td>Glc/A</td>
<td>12.53 ± 4.88</td>
<td>12.44 ± 5.67</td>
<td>16.71 ± 8.90</td>
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<tr>
<td>V/A</td>
<td>4.36 ± 2.62</td>
<td>4.65 ± 3.61</td>
<td>7.10 ± 3.50</td>
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<tr>
<td>A/L</td>
<td>1.455 ± 1.166</td>
<td>1.263 ± 1.152</td>
<td>0.773 ± 0.485</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.37 ± 1.05</td>
<td>1.75 ± 0.93</td>
<td>5.78 ± 5.14</td>
</tr>
<tr>
<td>HOMA-AD</td>
<td>160 ± 111</td>
<td>111 ± 75</td>
<td>360 ± 392</td>
</tr>
<tr>
<td>AR</td>
<td>0.91 ± 0.33</td>
<td>1.09 ± 0.33</td>
<td>1.12 ± 0.31</td>
</tr>
<tr>
<td>IRAR</td>
<td>2.68 ± 0.97</td>
<td>3.03 ± 1.01</td>
<td>3.60 ± 1.15</td>
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</table>

*a*: Statistically significant for non-MetS women with respect to non-MetS men ($P < 0.05$).

*b*: Statistically significant for MetS women with respect to MetS men ($P < 0.05$).

*c*: Statistically significant for MetS men with respect to non-MetS men ($P < 0.05$).

*d*: Statistically significant for MetS women with respect to non-MetS women ($P < 0.05$).
and HOMA-IR ($r = -0.569$, $P = 0.034$). In addition, the correlations of AR with age ($r = 0.628$, $P = 0.016$), PP with resistin ($r = 0.568$, $P < 0.034$), AR ($r = 0.616$, $P = 0.019$), and IRAR ($r = 0.547$, $P < 0.043$), and of A/L with SBP ($r = -0.559$, $P = 0.038$), were obtained. In women with MetS ($n = 31$), WC was positively correlated with age ($r = 0.567$, $P = 0.001$), and V/A with AR ($r = 0.526$, $P = 0.002$) and with IRAR ($r = 0.478$, $P = 0.007$). A/L was negatively correlated with HOMA-AD ($r = -0.366$, $P = 0.043$) for the same group.

Of the MetS patients, 28 had normal glucose levels and 17 had high glucose levels. Both groups had significantly higher ($P < 0.01$) TG/Glc ($2.64 \pm 1.04$ and $1.50 \pm 0.93$, respectively) values than the controls ($0.86 \pm 0.34$). Table 1 shows the values of the parameters in the control, the MetS, and the MetS-HGL groups. When the MetS-HGL group was compared with the controls, a similar significance was obtained as in the comparison of the total MetS group with the control group, but with one exception: Glc/I did not show a significant difference. In the MetS-HGL group, insulin positively correlated with resistin ($r = 0.536$, $P < 0.028$), AR ($r = 0.583$, $P = 0.014$), and IRAR ($r = 0.691$, $P = 0.002$); Glc/A had a positive correlation with age ($r = 0.523$, $P = 0.031$), SBP ($r = 0.490$, $P = 0.046$), PP ($r = 0.562$, $P < 0.019$), HOMA-IR ($r = 0.495$, $P = 0.043$), and HOMA-AD ($r = 0.696$, $P = 0.002$); and visfatin was inversely related to age ($r = -0.500$, $P = 0.041$).

4. Discussion
Although affected levels of adipokines were observed in MetS, the ratios of the levels of adipokines gave more significant results.

Leptin and visfatin levels increased significantly, but adiponectin levels decreased (approaching borderline significance, $P = 0.052$) in MetS. Resistin increased, but not significantly. Women with MetS showed significant increases in the levels of leptin and visfatin, and a decrease in adiponectin; men with MetS showed a significant increase in visfatin only. Increased leptin level suggests the development of leptin resistance (17). Two important proinflammatory regulators, resistin and visfatin, interfere with the central regulation of insulin sensitivity (4). Elevated resistin levels have been found in obesity, visceral fat, insulin resistance, and type 2 diabetes (18). The increased visfatin levels may promote low-grade systemic inflammation associated with MetS (19); they correlate with increased visceral adiposity and hyperglycemia (20). Plasma adiponectin levels decrease in insulin resistance, proinflammatory and prothrombotic states, and endothelial cell dysfunction (17). Adiponectin leads to increase in fatty acid combustion and energy consumption, but decrease in TG content in the liver and skeletal muscles, thereby increasing in vivo insulin sensitivity (21).

We did not observe any significant difference in adipokine levels between men and women in the MetS or control groups. Moreover, most of the other parameters, including insulin levels, determined in this study did not show any significant difference. Insulin and age are very important parameters for adipokines (4,17,22,23). The insignificant levels in adipokines may result from insignificant differences in age and in insulin levels.

In the MetS group, leptin had a statistically significant positive correlation with insulin ($P < 0.05$). It has been suggested that a positive relation between leptin and insulin levels could be found in patients with highly disturbed endogenous insulin secretion, and it seems likely that insulin regulates leptin (22). A significant negative correlation was observed between visfatin and age in the MetS group (mainly in the MetS-HGL group). An earlier study also reported an inverse relation between visfatin levels and age, with a decrease in visfatin by 4.1 ng/mL for each year of age (23).

Elevated levels of V/A, AR, and IRAR were obtained in MetS. In addition, AR and IRAR showed positive correlations with insulin, mainly in the MetS-HGL group. AR and IRAR indices were reported as good indicators for long-term metabolic status, and the AR index is more strongly associated with increased risk of type 2 diabetes and MetS than adiponectin and resistin levels alone (15). Adiponectin and visfatin have opposite effects on insulin resistance (24). Earlier, a negative correlation between adiponectin and HOMA-IR (25) and a positive correlation between visfatin and HOMA-IR (26) were reported. V/A has not been analyzed before. In our study, V/A showed a positive correlation with AR and IRAR indices. The opposite effects of adiponectin and visfatin, and their relationship with insulin resistance indices (AR and IRAR), suggest that the V/A ratio might be one of the indicators of insulin resistance.

Decreased A/L was observed in all MetS subjects, but it was statistically significant only in women. It was reported that the A/L ratio gradually decreases with the number of MetS components (27). In addition, it is suggested that the A/L ratio is more effective in relevance as a parameter of insulin resistance compared with adiponectin or leptin alone, and a more sensitive and reliable marker of insulin resistance than HOMA-IR in patients with type 2 diabetes (28). Moreover, the leptin to adiponectin ratio is identified as a useful parameter to assess insulin resistance in patients with and without diabetes (29), and this ratio may serve as a potential athorogenic index in obese type 2 diabetic patients (30). In our study, A/L showed inverse relation with insulin and resistin in the MetS group, with SBP in MetS men, and with HOMA-AD in MetS women. Leptin stimulates the renin–angiotensin and the sympathetic nervous systems (31), and high leptin levels induce

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systemic and intrarenal oxidative stress, which may lead to hypertension (32). Adiponectin levels are modulated by the renin–angiotensin system (33). Therefore, the blockade of the renin–angiotensin system causes an increase in serum adiponectin concentration. Hypoadiponectinemia is associated with insulin resistance in patients with essential hypertension (34). In the current study, the decreased level and negative relation of A/L with insulin suggests that A/L might be used as an insulin sensitivity index.

Increased Glc/A was found in MetS patients (significantly in women) and showed positive correlations with HOMA-IR and HOMA-AD in the MetS-HGL group. It appears that the ratio of fasting Glc/A may be an important factor in prediabetes, which involves declined insulin sensitivity (35). HOMA-AD is also found to be an adequate tool for determining insulin resistance among obese children with MetS (36). In the current study, Glc/A was also correlated with SBP and PP in the MetS-HGL group, and so was PP with resistin, AR, and IRAR in the MetS men. The increase in PP is associated with an increase in large arterial stiffness and the increased arterial stiffness in MetS might be due to insulin resistance, endothelial dysfunction, atherogenic alterations, neurohormonal abnormalities, and hypercoagulability (37). Impaired fasting glucose increases arterial stiffness by causing glycation of matrix proteins and accumulation of advanced glycation end products (38).

A significantly decreased Glc/I ratio was observed in the MetS group, but a slightly increased (not significant) Glc/I ratio was noted in the MetS-HGL group. This ratio was negatively correlated with SBP, DBP, MAP, and HOMA-IR in men. One study reported that the fasting Glc/I ratio is an appropriate index of insulin sensitivity, but it becomes apparent only when fasting glucose levels are abnormal (39). Similarly, another study reported that it is a weak insulin sensitivity index and is probably similar to 1/insulin in nondiabetic subjects (40). According to our results, it may reflect insulin sensitivity if the individuals do not have high glucose levels.

TG/HDL-C ratio increased in the MetS subjects and was higher in men than in women. This ratio has been identified as a reliable marker of insulin resistance in overweight patients (41). Since insulin affects TG and HDL-C metabolism, the presence of hypertriglyceridemia, low HDL-C concentrations, and high TG/HDL-C ratio might be associated with insulin resistance (42). However, we did not obtain any correlation of this ratio with insulin resistance parameters.

To our knowledge, TG to glucose ratio has not been analyzed in the literature. In this study, TG/Glc was significantly higher in the MetS and the MetS-HGL groups when compared with the controls. Hyperglycemia and hyperlipidemia are important risk factors for diabetes-accelerated atherosclerosis (43). Alterations in glucose and lipid metabolism may cause endothelial dysfunction, leading to vascular remodeling and subsequent atherosclerosis (44). It was also reported that subjects with hypertriglyceridemia were more likely to have hyperglycemia than were those with normal TG (45). Glycerol is released from the breakdown of TG and is converted to glucose by the liver (46). In the present study, the TG/Glc ratio did not show any correlation with other parameters in the MetS-HGL group. However, the elevated values of this ratio, even at high glucose levels, indicate that hypertriglyceridemia is a more predominant abnormality than hyperglycemia in MetS. Thus, this ratio might be a novel MetS marker. However, a limitation of this study was the small number of patients. Thus, to confirm TG/Glc and V/A as novel markers, further studies with larger numbers of subjects and multiple regression analyses are needed. When MetS subjects were compared with controls, women showed significant differences from men in nearly all parameters, which might be due to the small number of men in the study.

In conclusion, the adipokine levels were affected in MetS, but combining the values of adipokines, insulin resistance/sensitivity parameters, and other MetS criteria gave more significant differences between groups. It is well known that the parameters studied might affect, interact with, and/or interfere with each other, so instead of depending on a single parameter, the use of combinations might help improve the evaluation of insulin resistance/sensitivity in MetS.

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