Increased Chemerin and Decreased Omentin-1 in Both Adipose Tissue and Plasma in Nascent Metabolic Syndrome

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Context: Adipose tissue dysregulation causing aberrant adipokine secretion contributes toward the proinflammatory state of metabolic syndrome (MetS). However, there are scant data on the role of novel adipokines in MetS.

Objective: The aim of this study was to determine the levels of circulating and adipose tissue-secreted adipokines, chemerin, omentin-1, resistin, and visfatin in nascent MetS patients without diabetes or cardiovascular disease and to determine their relation with features of MetS.

Design and Setting: Subjects with MetS and gender- and age-matched controls were recruited after informed consent. Fasting blood samples and gluteal subcutaneous adipose tissue (SAT) biopsies were obtained.

Main Outcome: SAT-secreted and plasma levels of chemerin, omentin-1, resistin, and visfatin were quantitated.

Results: There was significantly higher circulating as well as SAT-released chemerin in nascent MetS compared to controls, which persisted after adjustment for body mass index, waist circumference, and age. Also, both SAT-released and plasma levels of omentin-1 were significantly lower in MetS compared to controls, and the significant differences persisted after adjustment for age, body mass index, or waist circumference. No significant differences were observed in the levels of circulating visfatin as well as SAT-secreted resistin and visfatin. Chemerin correlated significantly with high-sensitivity C-reactive protein, homeostasis model of assessment for insulin resistance, triglycerides, and blood pressure, and inversely with omentin and high-density lipoprotein cholesterol. Omentin correlated significantly with high-density lipoprotein cholesterol and inversely with glucose and triglycerides.

Conclusions: We make the novel observation of abnormal circulating and gluteal SAT-secreted chemerin and omentin-1 levels in nascent MetS, which could confer a higher risk for diabetes and cardiovascular disease. (J Clin Endocrinol Metab 98: E514–E517, 2013)
Nascent MetS is a term describing MetS patients who do not have the complications of diabetes and/or CVD as we reported previously (5). Recently, in patients with nascent MetS without the confounding of diabetes or CVD, we made the novel observation that they exhibit a dysregulation of subcutaneous adipose tissue (SAT) biology manifesting as abnormal secretion of established adipokines, cytokines, and chemokines (6). Most of these aberrations persisted after adjusting for adiposity, suggesting that MetS is a high-risk state of obesity.

However, there continues to be a paucity of data on adipose tissue biology and plasma adipokines in nascent MetS without diabetes and CVD. A study of this population can prove instructive in elucidating the role of adipose tissue in the pathobiology of early nascent MetS, and hence provide insights with respect to therapeutic strategies. To this end, we now report our findings regarding the levels of the circulating and adipose tissue-secreted more novel adipokines, chemerin, omentin-1, resistin, and visfatin in nascent MetS patients without concomitant diabetes or CVD.

**Subjects and Methods**

Informed consent was obtained from all participants in the study, which was approved by the Institutional Review Board at the University of California, Davis. Furthermore, all human investigations were conducted according to the principles expressed in the Declaration of Helsinki. MetS was defined using the modified criteria of the National Cholesterol Education Program Adult Treatment Panel III as described previously (5–7). All the modified criteria of the National Cholesterol Education Program were satisfied. Subjects were recruited from Sacramento County through fliers and advertisements in the newspaper. Subjects included in this report were on antihypertensive medications (diuretics). Furthermore, all the MetS subjects included in this report were on antihypertensive medication. Three of the MetS groups were frequency-matched to achieve balance for gender and age within 10 years.

For both groups, detailed exclusion criteria were as reported previously (5, 6). Importantly, none of the subjects had diabetes or any chronic inflammatory diseases, nor were on any anti-inflammatory, hypolipidemic, or hypoglycemic drugs. None of the controls were on antihypertensive medication. Three of the MetS subjects included in this report were on antihypertensive medications (diuretics). Furthermore, all the MetS groups had C-reactive protein (CRP) levels <10 mg/L, normal complete blood counts, fasting glucose concentrations between 100 and 125 mg/dL, and a glycated hemoglobin <6.5%.

After a history and physical examination, a fasting blood sample was obtained from all participants. Complete blood count, plasma lipid and lipoprotein profile, creatinine, plasma transaminases, glucose, and TSH were assayed by standard laboratory techniques in the Clinical Pathology Laboratory. Insulin levels were assayed by ELISA (Linco Research Inc, St Charles, Missouri) and a homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated from glucose and insulin levels as described previously (5, 6). Chemerin, resistin, visfatin, and omentin-1 levels were measured in plasma in duplicates employing sensitive and specific quantitative sandwich ELISA using reagents from MyBioSource (San Diego, California). The coefficient of variation for both chemerin and resistin was 11%, whereas the coefficients of variation for omentin and visfatin were 7% and 14%, respectively.

SAT biopsies were also performed on all subjects as described previously (6). Briefly, SAT was obtained from the gluteal region; approximately 4–6 ml of fat and fluid were aspirated, washed, and then placed in transport medium. The aspirated SAT was weighed in a balance, then minced into fine (<10 mg) pieces, and resuspended in adipose tissue culture medium containing M199 (Invitrogen [Life Technologies], Grand Island, New York) supplemented with 50 μg/mL gentamicin and penicillin-streptomycin as described previously (6). The SAT was then incubated in multiple wells for 24 hours, and the cell supernatants were collected. All ELISAs were performed as described above for the plasma, and the results were normalized per milligram of cell protein.

Data are expressed as mean ± SD or, for skewed variables, as median and interquartile range. Log transformations were applied to skewed data before parametric analyses. Comparisons between the control and MetS groups were made with 2-sample t tests and analysis of covariance to adjust for body mass index (BMI) and waist circumference (WC). In both the control and MetS groups, Spearman’s rank correlation coefficients were computed to assess the association between the outcome variables and metabolic status. Data were analyzed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

**Results**

Table 1 shows the salient characteristics of the control and MetS groups. All five features of the MetS were different between the 2 groups. Also, patients with MetS were more insulin resistant and had higher levels of high-sensitivity CRP (hsCRP).

The circulating levels of chemerin were significantly higher in MetS compared to controls, and this persisted after adjustment for age and BMI or WC (Table 1) (P = .0005). There were significantly lower levels of plasma omentin-1 in MetS compared to controls (P = .004); the differences were significant when adjusted for BMI or WC (P = .03) (Table 1). There were also higher levels of circulating resistin in MetS compared to controls, which did not persist after adjustment for BMI or WC. Plasma visfatin levels were not significantly different between the 2 groups.

As shown in Figure 1, there was also a significantly higher release of chemerin from SAT, which persisted after adjustment for BMI or WC and age. In addition, there was a significantly lower secretion of omentin from SAT, which persisted after adjustment for both age and BMI or WC. However, the secretion of both resistin and visfatin from SAT
otherwise stated. Plasma chemerin correlated significantly (P < .05) with SAT chemerin (r = .44), hsCRP (r = .28), HOMA-IR (r = .42), TG (r = .41), systolic BP (r = .28), omentin (r = -.42), and HDL-C (r = -.037). Also, both circulating and SAT omentin-1 levels correlated significantly (r = .44; P < .05). Plasma omentin-1 correlated significantly with glucose (r = -.38), TGs (r = -.48), and HDL (r = .52).

Discussion

To date, there are sparse data on novel adipose tissue and plasma adipokines in nascent MetS, a high-risk obesity state and antecedent to both diabetes and CVD. Hence, the aim of this study was to determine the levels of the circulating and adipose tissue-secreted adipokines chemerin, omentin-1, resistin, and visfatin in nascent MetS patients at this early stage, without concomitant diabetes or CVD, and to elucidate their relation with features of MetS.

Chemerin is a novel adipokine that is produced by both adipose tissue and liver, is a chemoattractant for immune cells such as macrophages, and appears to promote adipocyte differentiation (8). It is a ligand for the orphan G protein-coupled receptor chemokine-like receptor 1 (CMKLR1) (8). Chemerin levels have also been shown to be higher in obesity, some features of MetS, diabetes, and activity score for nonalcoholic fatty liver disease (8–10) and induces insulin resistance in skeletal muscle, the major site of peripheral insulin resistance (11). We make the novel observation that both plasma and gluteal SAT levels of chemerin are higher in nascent MetS without the confounding effects of diabetes and CVD, suggesting that chemerin could be involved early in the pathogenesis of this disorder.

Based on our study, it appears in subjects with MetS that higher plasma chemerin level emanates largely from the adipose tissue (because both plasma and SAT levels were higher and correlated); however, we cannot exclude the contribution of other sources of chemerin production such as the liver, although none of our patients had higher transaminase levels. It needs to be pointed out that visceral adipose tissue is not a major source of chemerin (12), and thus the present study highlights the contribution of SAT to circulating chemerin and its use as a potential biomarker of SAT dysregulation.

Table 1. Salient Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 30)</th>
<th>MetS (n = 45)</th>
<th>P Value Controls vs MetS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. of females/males</td>
<td>23/7</td>
<td>36/9</td>
<td>.78</td>
</tr>
<tr>
<td>Age, y</td>
<td>48 ± 12</td>
<td>54 ± 10</td>
<td>.03</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>92 ± 14</td>
<td>108 ± 13</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.1 ± 4.9</td>
<td>35.5 ± 6.4</td>
<td>&lt;.0003</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>120 ± 12</td>
<td>132 ± 11</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 ± 9</td>
<td>82 ± 9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>88 ± 7</td>
<td>100 ± 11</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>186 ± 34</td>
<td>196 ± 29</td>
<td>19</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>82 ± 36 (range, 33–199)</td>
<td>158 ± 62 (range, 50–310)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>53 ± 15</td>
<td>39 ± 10</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>116 ± 27</td>
<td>125 ± 22</td>
<td>.12</td>
</tr>
<tr>
<td>hsCRP, mg/dL</td>
<td>1.3 (5.4, 0)</td>
<td>3.1 (1.6, 5.4)</td>
<td>.006</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.1 (1.0, 2.8)</td>
<td>2.8 (1.9, 5.1)</td>
<td>.0001</td>
</tr>
</tbody>
</table>
| Plasma chemerin, ng/mL    | 271 ± 53, n = 20  | 366 ± 64, n = 37 | <.0001 (.0005)^
| Plasma omentin, ng/mL     | 27 ± 14, n = 16   | 16 ± 5, n = 16 | .004 (.03)^
| Plasma resistin, ng/mL    | 1.8 (1.5, 2.5), n = 21 | 2.4 (1.7, 3.1), n = 31 | .04 (.07)^
| Plasma visfatin, ng/mL    | .57 (.38, .71), n = 22 | .59 (.31, .96), n = 36 | .14 (.13)^

Abbreviation: LDL-C, low-density lipoprotein cholesterol. Results are presented as mean ± SD or median (25th percentile, 75th percentile), unless otherwise stated.

*a P value adjusted for age, BMI, and WC.

Figure 1. Secretion of chemerin and omentin-1 from gluteal SAT. Depicted P values were adjusted for BMI and age (data still significant when also adjusted for WC). Data are expressed as nanograms/milligrams cell protein.
This important observation needs to be confirmed in other cohorts. Thus, we add to the literature by showing higher SAT and plasma chemerin independent of obesity in nascent MetS and also confirm significant correlation with insulin resistance, inflammation, BP, and dyslipidemia in nascent MetS, suggesting a potential role in MetS and its sequelae (8–11).

Omentin is predominantly expressed and secreted by visceral adipose tissue (13, 14) and appears to have insulin-sensitizing actions (14). Furthermore, omentin levels are lower with both obesity and diabetes (14, 15). We also document for the first time lower levels of omentin in nascent MetS in both SAT and plasma. Lower omentin levels persisted after correction for obesity in both plasma and SAT. Because adipose tissue is the major source of omentin, we believe that the lower secretion from SAT establishes omentin deficiency in MetS also. Thus, we add to the published literature by documenting lower omentin release from SAT in nascent MetS. Omentin levels significantly correlated with glucose \( r = −.43 \), TGs \( r = −.50 \), and HDL-C \( r = .53 \), all features of MetS, but not with CRP and HOMA-IR. Furthermore, although we showed higher plasma resistin concentrations in the MetS individuals (which corrected with adiposity), we did not demonstrate higher SAT resistin levels. Thus, we can conclude that this adipokine, which in humans arises mainly from activated leukocytes (16), is a marker for the higher leukocyte activity we reported previously (5, 7).

Moreover, because visfatin levels were not different in MetS vs control subjects, we cannot confirm a role for visfatin in MetS.

The role of gluteal adipose tissue was previously thought to be protective or “good fat” (17). In the present study (higher chemerin and lower omentin-1) and our previous more extensive report on the adipokine repertoire (5), we clearly show adipokine dysregulation in gluteal fat possibly contributing to both the higher inflammation and insulin resistance. Hence, additional studies are needed to confirm that indeed all fat depots including the gluteal compartment are detrimental if studied carefully, as in the present report and our previous study (5).

In conclusion, we make the novel observation that there is dysregulation in gluteal adipose tissue, and both chemerin and omentin in nascent MetS could contribute to the progression of both diabetes and CVD in MetS subjects. Future studies should test the role of chemerin as a biomarker, longitudinally with respect to the development of both diabetes and CVD in MetS.

Acknowledgments

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References


