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# Association Between Omentin, Visfatin and Insulin-Like Growth Factor-1 in Women With Metabolic Syndrome

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**Background:** Adipokines that are produced by adipose tissue have extensive effects on carbohydrate and lipid metabolism and also on the pathogenesis of the metabolic syndrome (MetS).
**Objectives:** This study aimed to measure the concentrations of omentin-1, visfatin and insulin-like growth factor-1 (IGF-1) as likely markers of metabolic syndrome and also to demonstrate their associations in women with MetS.
**Materials and Methods:** Eighty women with MetS and eighty healthy women as controls participated in this study. Blood pressure, waist circumference, body mass index (BMI), and serum biochemical parameters were determined in all subjects. The serum level of IGF-1, omentin-1 and visfatin were assessed using the enzyme linked immunosorbent assay (ELISA). The association between omentin, visfatin and IGF-1 was also determined in these women.
**Results:** Significantly lower levels of omentin-1 and IGF-1 were observed in MetS subjects compared to the controls ($P = 0.009$ and $< 0.001$ respectively). However, a significant difference was not observed in visfatin concentration between the two studied groups ($P = 0.67$). A positive association was observed between omentin-1, visfatin and IGF-1 in the MetS group.
**Conclusions:** Our findings indicated a lower level of both omentin-1 and IGF-1 in women with MetS; this might play a role in the pathogenesis of MetS. Furthermore, the main finding of the current investigation was the association between omentin, visfatin and IGF-1; however determining the molecular mechanism of the observed relationships needs further studies.

*Keywords:* IGF-I; Metabolic Syndrome; Iran

## 1. Background

Nowadays metabolic syndrome (MetS) is a worldwide epidemic and bears a high socioeconomic cost (1). Combinations of unhealthy diet, sedentary lifestyle and genetic factors have been known as the main risk factors for the incidence of MetS. Metabolic syndrome can augment the risk of some chronic diseases such as type 2 diabetes (T2D) and cardiovascular disease (2, 3). In addition to clinical symptoms, biochemical and physiological abnormalities are observed in these patients. These disorders include: abdominal obesity, dyslipidemia, high blood pressure and disturbed glucose homeostasis, insulin resistance, chronic inflammation, procoagulation and impaired fibrinolysis (4). Chronic inflammation and increase in inflammatory cytokines are triggering pathophysiological factors in development of MetS. Adipokines that are produced by adipose tissue have extensive effects on carbohydrate and lipid metabolism and also in the pathogenesis of MetS (5). A characteristic imbalance of adipokine profile has been observed in obese subjects and/or those with MetS (6). Omentin as a new adipokine is encoded by two genes (1 and 2). Gene expression of omentin in visceral adipose tissue is higher and more selective compared to subcutaneous adipose tissue. The major form of omentin in human plasma is omentin 1. Omentin 1 gene expression in adipose tissue and its plasma level diminish in obesity. Furthermore, there is a positive correlation between plasma omentin levels and plasma adiponectin and high-density lipoprotein (HDL). On the other hand plasma omentin level is inversely correlated with waist circumference and BMI. Omentin is known as an insulin-sensitizing adipokine and low levels of it is present in patients with diabetes and subjects with glucose intolerance or insulin resistance (7, 8). Visfatin (pre-B-cell colony-enhancing factor, PBEF) is another novel adipokine, predominantly expressed in visceral adipose tissue; it is upregulated in obese animals and humans. Visfatin has enzymatic activity, and the rate-limiting step in biosynthesis pathway of nicotinamide adenine dinucleotide in mammals is catalyzed by this protein (9). Visfatin binds to insulin receptors and promotes insulin sensitivity. Increased plasma visfatin has been reported in T2D and obese subjects. Although it seems to have a compensatory role, there is insufficient response in obesity-induced insulin resistance (10). Visfatin is also synthesized

in response to inflammatory stimuli and can upregulate cytokines (11). However, its' molecular and biochemical features and also its pathophysiological role in humans remain unknown. Another important element that may have role in MetS pathogenesis is insulin-like growth factor-1 (IGF-1). Growth regulation and cellular proliferation are routes mediated by IGF-1 (12). It has been shown that IGF-1 has similar structure to insulin and through binding and activation of IGF-1 receptor, it might diminish the insulin resistance in patients with T2D, obesity and hyperlipidemia (13). Reduction in IGF-1 and its binding proteins (especially IGFBP-1) have been observed to correlate with MetS and obesity, disturbed glucose metabolism, high blood pressure, disturbed lipid profile and cardiovascular disease (13, 14). Nevertheless, there is also some inconsistency in the association between IGF-1 level and MetS (14, 15). Furthermore limited researches have been carried out to examine the correlation between visfatin, omentin-1 and IGF-1 in patients with MetS.

## 2. Objectives

This study was designed and performed to identify the possible relationships between visfatin, omentin-1 and IGF-1 in MetS. To achieve this goal we measured the serum concentrations of these factors and examined their correlations in female patients with MetS.

## 3. Materials and Methods

### *3.1. Subjects and Anthropometric Evaluation*

This study was performed in Hamadan (Iran) from June 2011 to December 2012, with eighty female participants with metabolic syndrome. Diagnosis of metabolic syndrome was based on the International Diabetes Federation (IDF, 2005) criteria. During the physical examination of patients their basic information including age, gender, weight and height were recorded. Also BMI and waist circumference were measured and systolic and diastolic blood pressures were determined. Signed informed consent was obtained from all participants. The exclusion criteria were as follows: presence of acute or chronic infective, autoimmunity, gastrointestinal, hepatic and renal diseases. Also subjects with a history of secondary hypertension, heart failure, drug abuse, and smoking were expelled from the study. The control group consisted of 80 age- and sex-matched healthy subjects who had referred to the clinic for a routine physical check-up. They did not have a history of cardiac disease, hypertension or diabetes. The study protocol was approved by the Clinical Research Ethics Committee of Hamadan University of Medical Sciences. Also, the principles outlined by the Helsinki Declaration were considered.

### *3.2. Biochemical Assays*

Venous blood samples with a volume of 5-7 mL were collected between 8 and 9 am, after overnight fasting (12 hours) and the sera were separated using standard procedures and kept frozen (-80°C) until analysis. Serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, as well as triglycerides were determined using the enzymatic method and an autoanalyzer (Hitach 911, Germany). The plasma concentrations of visfatin were assayed by a commercial ELISA kit (Adipogen Inc. Korea), with a sensitivity of 30 pg/mL and intra- and inter-assay coefficients of variations of 5.6% and 5.9%, respectively. An ELISA kit containing natural human omentin-1 antibody from Enzo Life Science (Germany) was used to assay serum levels of omentin-1 and the procedure was performed according to the manufacturer's instructions. In this assay the detection limit was 0.4 ng/mL (range 0.78 to 50 ng/mL). Intra-and inter-assay coefficients of variation were between 4.5% and 9.7%. Total IGF-1 was measured using the enzyme immune assay (EIA) kit (Enzo Life Science, Germany). Inter-assay and intra-assay coefficients of variation (CV) were 7.1% and 5.8%, respectively. These three factors were measured in duplicates in a single experiment.

### *3.3. Statistical Analysis*

Data are presented as mean ± standard deviation (SD). The normality of obtained data was checked using the Kolmogorov-Smirnov test (KS-test). t-test and chi-square test were used to compare baseline characteristics between the two studied groups. The associations between visfatin, omentin and IGF-1 were determined using Pearson's correlation coefficient. $P < 0.05$ was considered significant. Statistical analysis was carried out using the SPSS software (Version 16.0).

## 4. Results

Both groups of women, i.e. metabolic syndrome and control, were of similar age (mean 40.4 and 40.1 years, respectively). As shown in Table 1, the waist circumference, BMI and systolic blood pressure were significantly higher in the MetS group than the control group ($P < 0.001$). However diastolic blood pressure was higher in the metabolic syndrome group, yet the difference was not significant ($P = 0.174$, Table 1). Serum concentrations of total cholesterol, triglycerides, LDL-C and glucose were significantly higher ($P < 0.001$), and concentration of HDL-C was not significantly lower in the MetS group than in the control ($P = 0.241$, Table 1). The serum IGF-1 and omentin concentrations were markedly lower in the patients with MetS than the control ($P < 0.001$ and $= 0.009$, respectively Figure 1 A-B), whereas visfatin did not differ significantly between the studied groups ($P = 0.67$, Figure 1 C).

In the correlation analysis of the obtained data from MetS women, we observed a positive association between omentin and IGF-1 levels ($r = 0.38$, $P = 0.001$), omentin and visfatin ($r = 0.32$, $P = 0.01$), and visfatin and IGF-1 ($r = 0.21$, $P = 0.03$).

**Table 1.** Comparison of Clinical Parameters Between Metabolic Syndrome and Control Subjects [a, b]

| Variables | Controls | Metabolic Syndrome Patients | P Value |
|---|---|---|---|
| **Age, y** | 40.1 ± 5.5 | 40.4 ± 6.3 | 0.39 |
| **Waist circumference, cm** | 85 ± 13 | 101 ± 10 | <0.001 |
| **Body mass index, kg/m$^2$** | 26 ± 4 | 31 ± 5 | <0.001 |
| **Systolic blood pressure, mm Hg** | 11.3 ± 1.2 | 12.6 ± 2.1 | <0.001 |
| **Diastolic blood pressure, mm Hg** | 7.7 ± 0.7 | 10.1 ± 1.3 | 0.174 |
| **FBS, mg/dL** | 85 ± 8 | 100 ± 28 | 0.001 |
| **TG, mg/dL** | 114 ± 30 | 214 ± 107 | <0.001 |
| **tChol, mg/dL** | 167 ± 27 | 203 ± 52 | <0.001 |
| **HDL-C, mg/dL** | 48 ± 7 | 44 ± 20 | 0.241 |
| **LDL-C, mg/dL** | 94 ± 28 | 127 ± 36 | <0.001 |

[a] Abbreviations: FBS, fasting blood sugar; HDL-C, high density lipoprotein- cholestrol; LDLc, low density lipoprotein-cholestrol; TG, triglycerides; tChol, total cholesterol.
[b] Data are presented as Mean ± SD.

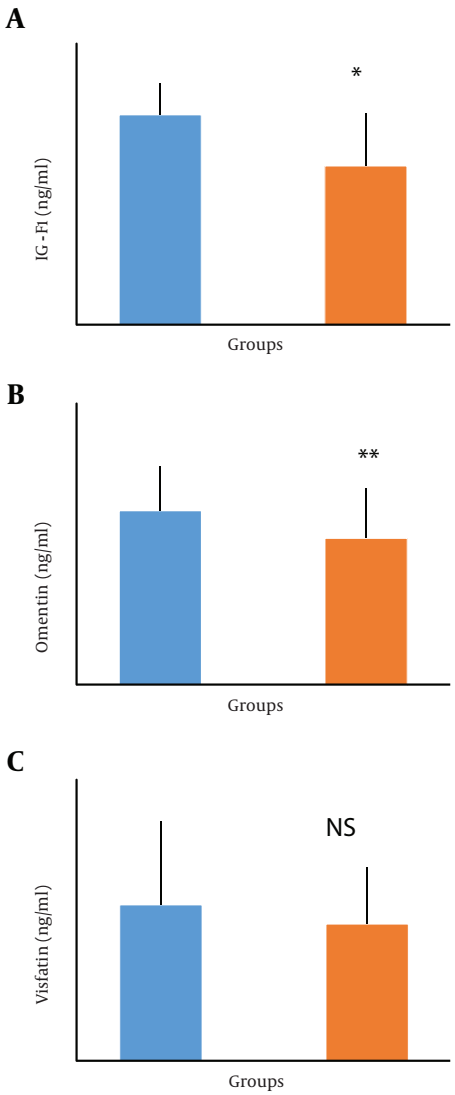


**Figure 1.** Serum IGF-1 (A), Omentin (B) and Visfatin (C) Levels in Patients With Metabolic Syndrome and Healthy Controls (n = 80)

## 5. Discussion

The prevalence of MetS is rising in all countries; one possible reason is epidemic of obesity in most populations (1, 2). In the current study, risk factors for the metabolic syndrome (16) including high triglyceride, LDL-C, total cholesterol, fasting blood glucose, systolic blood pressure, waist circumference and BMI were significantly higher in women with MetS. Nevertheless diastolic blood pressure and HDL-C were not significantly different between subjects with MetS and healthy controls. Since a significant positive correlation between age and MetS has been reported (17), we matched the age of subjects to exclude the effect of this variable. Furthermore since women and men have fairly different metabolic and endocrine profiles and it does not seem logical to allocate them to a single category; our study was focused only on females. Adipocytes and adipokines probably play critical roles in MetS. In the recent years the number and varieties of adipokines are growing, therefore understanding the diverse effects of these identified adipokines are important. The other important issue that must be elucidated is the interaction between these bioactive molecules (18). Visfatin and omentin are remarkable adipokines that have recently been investigated for their different aspects. Insulin-like growth factor-1 is another important element that may have a role in MetS pathogenesis. In this research we assessed the association between visfatin, omentin-1 and IGF-1 in patients with MetS. Our findings demonstrated that women with MetS have lower levels of omentin and IGF-1 compared to those without MetS and this difference was statistically significant. In our study we did not observe differences in visfatin level between subjects with and without MetS. There was a positive significant correlation between omentin, visfatin and IGF-1 levels in women with MetS. We did not find any study that has reported an association between omentin, visfatin and IGF-1 in patients with MetS. Nevertheless, there are some reports showing a relationship between visfatin, omen-

tin and MetS but their results are divergent (19, 20). Some studies have found elevated circulating levels of visfatin in obese subjects (19). Other studies, similar to our results, have not found any significant differences in visfatin levels between patients with MetS and healthy controls (21). Moreover, Zhong et al. reported elevation in serum visfatin in patients with MetS particularly in those with carotid plaques (22). Also Kim et al. showed high levels of visfatin in postmenopausal women with MetS (23). These different findings are difficult to explain based on the present knowledge, consequently the association between MetS and visfatin remains to be further elucidated. The reasons for these contradictory results can be differences in patients' characteristics and use of non-homogenous groups in different studies (24). Also, the limited number of studied subjects, differences in sample collection and the assay methods can be other reasons (24). Moreover, race can play a role in these differences; our studied population consisted of only one race. Our findings of positive correlations between visfatin and IGF-1 levels in subjects with MetS support visfatin proinflammatory action. Role of visfatin as a proinflammatory cytokine has been reported previously (25). According to the obtained data we can only hypothesize that decreased visfatin levels in subjects with MetS may inhibit the production of IGF-1, and in turn worsen MetS conditions. Therefore, it seems that the role of visfatin in metabolic syndrome is complex and needs further investigations. The observed significant decrease in serum levels of omentin-1 in subjects with MetS is another important finding of our study. Our findings confirm the results of previous studies (20, 26). Liu et al. reported lower levels of omentin-1 in patients with MetS compared to controls and indicated a close relationship between this element and MetS (27). We can postulate that the reduction in omentin-1 levels in subjects with MetS may be due to peripheral adiposity. Insulin resistance and hyperglycemia are the core processes and important risk factors for MetS, which significantly reduce the expression of omentin mRNA and its translation (28). Therefore, omentin-1 probably depresses the metabolic syndrome process throughout glucose metabolism normalization. The weak correlation of visfatin versus IGF-1 and omentin can be due to the small number of subjects in this study and further studies are demanded to uncover the mechanism of associations between these factors in MetS. According to our findings we can suggest that lower level of IGF-1 can prognoses the MetS; this finding adds new light to what has been reported in the literature (29). Decrease in IGF-1production has been reported to be associated with some components of MetS; this is most likely due to an association with low glucose uptake and IGF-1 receptor upregulation (30). This event can lead to augment the development of hybrid insulin/IGF-1 receptors (30). The metabolic effects of IGF-1 that were observed in our study can be described by the interaction between signaling pathways (31). Insulin-like growth factor-1 may improve insulin resistance, both centrally and peripherally and also increase lipolysis and decrease body fat mass; this takes place by inhibition of insulin secretion that inhibits the lipogenic capacity of adipose tissue (31). However we found a relationship between IGF-1, omentin and visfatin in patients with MetS, while the exact molecular mechanisms between these elements remain to be revealed. As a limitation of our study we can point out that we did not evaluate the possible association between visfatin, omentin, IGF-1and MetS parameters in the studied women. There were also a limited number of subjects in our investigation; working on a larger sample size containing males and females may reveal more details. Since we prepared only a single sample to measure these variables, the results might not reflect the true levels of these elements and their daily changes in MetS patients. For consistency of the samples we used fasting serum samples to measure these elements, however fasting state may affect the level of these elements. Overall, in addition to the defined risk factors for MetS, the reduction in concentration of omentin-1 and IGF-1 is possibly involved in MetS pathogenesis and these factors might be considered as biomarkers for this disorder. The observed correlation between IGF-1, omentin and visfatin can be considered as the main deduction of our study. However further investigations on both sexes and in a larger population is required to explain the roles and mechanisms of action of visfatin, omentin and IGF-1 in MetS.

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## Authors' Contributions

Mohammad Taghi Goodarzi designed the study, performed the data analysis, prepared the manuscript, approved the final version and supervised the study. Shiva Borzuei performed the physical examination of patients, selected the candidates and interpreted the results. Azam Rezaei Farimani collected the data, prepared the manuscript and performed the biochemical analysis. Maryam Sohrabi performed the data analysis, acquisition of data, technical support and drafting of the manuscript.

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