Relationship between Serum Visfatin and Obesity in Lead-Exposed Obese Subjects and Patients with Osteoarthritis

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Abstract

Aim: To evaluate the relationship between serum levels of visfatin, lead (PB) and cadmium (Cd) in obese male subjects with osteoarthritis (OA). Methods: A total of 40 obese males (age: 25 - 55 years; BMI ≥ 30) participated in the study. They were subdivided into 3 groups; group A, 10 patients with OA; group B, 15 workers in gasoline filling stations; group C, 15 obese subjects without any apparent other health problems or chronic diseases. After overnight fasting, blood samples were collected from all participants to evaluate blood levels of Pb, Cd and HbA1c, in addition to serum visfatin, lipid profile, glucose and total antioxidant state (TAS). Results: Obese patients with OA have significantly higher BMI value (p < 0.05) than the other groups. Obese gasoline station workers demonstrate highest blood lead levels compared to the other groups. Serum visfatin levels in obese subjects with OA were significantly higher than that reported in the other groups. Blood lead contents and serum visfatin levels were positively and significantly correlated in the three groups, and greatest correlation coefficient value (r) was reported in obese OA patients followed by obese gasoline station workers and healthy obese subjects, respectively. BMI in obese healthy subjects shows weak positive and non-significant relationship with serum visfatin levels, while highly positive and significant correlation was reported between these two markers in obese gasoline station workers. However, BMI values and serum visfatin showed weak negative and non-significant correlation with serum visfatin levels in obese OA patients. Conclusion: Serum visfatin levels could be key regulators of obesity and OA, and an important partner with excessive environmental exposure to Pb in the pathogenesis of these disorders.

Keywords

Visfatin, Obesity, Osteoarthritis, Lead, Cadmium

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1. Introduction

Many reports highlighted direct signaling between subchondral bone and cartilage through the diffusion of mediators through the vasculature and microcracks [1]. This process enables transfer of soluble mediators that have the capability to modulate the functions of many cells at these sites [2]. During inflammatory conditions like osteoarthritis (OA), the synovium may be involved in the communication process through releasing chemical mediators that involved in joint damage and bone remodeling [3]. Adipokines are soluble mediators, which mainly released by adipose tissue, can be also produced by the synovium and significantly involved in OA pathogenesis [4] [5]. These adipokines played a crucial role in many immune, inflammatory and metabolic processes, including potential involvement in low-grade inflammation reported in obesity and might contribute to the associated metabolic diseases; accordingly they could be suggested as effective players during OA associated with obesity and/or exposure to other related etiologic factors [6] [7]. Recently, many researchers were interested in the adipokines visfatin [8], which was synthesized by adipose and many other tissues, including synovium and cartilage [9]. Although scanty data was available regarding the role of visfatin in OA, its production by IL-1β-stimulated OA chondrocytes has been previously reported [10]. Recently, extensive elevation in blood lead (Pb) levels in mice was associated with increased food intake, body weight, total body fat, and the possibility of excessive production of visfatin cannot be ruled out [11]. Obesity and extensive exposure to Pb were among the risk factors for development of OA, and many reports have shown that adipokines could play an important role in the progression of OA [3] [12]. In the present study, we aimed to address the relationship between plasma visfatin levels and blood levels of Pb and cadmium, and other metabolic markers in OA patients and obese subjects.

2. Methods

In this non-randomized cross-sectional study, 40 obese males, who routinely attended the out-patient clinic, Al-Hilla Teaching Hospital were included, and have body mass index (BMI) ≥ 30, calculated by dividing body weights over the square root of the body height; their age range was 25 - 55 years. They were categorized into 3 groups; the 1st group includes 10 obese patients which have been already diagnosed by senior rheumatologist with osteoarthritis according to the ACR criteria [13]; 2nd group includes 15 obese gasoline filling stations workers in Hilla City, Babylon who have a high chance to be exposed to heavy metals like Pb and Cd. The last group includes 15 obese subjects with no clinically defined illness or history of chronic diseases, and exposure to Pb and Cd were highly excluded. Adequacy of sample size was checked online using Evan’s Awesome A/B tool. The study was conducted during January-June 2015; the research protocol was approved by the local Research Ethics Committee at the College of Pharmacy, University of Baghdad, and informed signed consent was obtained from each subject before inclusion. The presence of any other pathologies like hypertension, diabetes and renal diseases was considered as an exclusion criteria. After reporting the demographic characteristics of each participant, fasting venous blood sample (10 ml) was obtained, and 5 ml was kept in plain tube, left to clot and centrifuged at 4000 rpm at 4°C for 10 min; the resulted serum was utilized for analysis of visfatin [14], total antioxidant capacity [15], lipid profile [16] [17] and fasting serum glucose levels [18]. The other 5 ml aliquot of blood was kept in heparinized tube and utilized for analysis of HbA1c [19], Cd and Pb levels with atomic absorption spectrometric method [20].

Statistical Analysis

Data analysis was performed using SPSS 15.0 software. The differences between the groups were evaluated with ANOVA followed by Benferronis’ post hoc test. The relationships between serum visfatin and other variables were assessed using the Pearson correlation analysis. The level of significance was accepted at $p < 0.05$.

3. Results

Primarily, no significant differences were reported between the mean ages of the three groups. Table 1 shows that obese patients with OA have significantly higher BMI value ($p < 0.05$) than the other groups, which are not significantly different with each other in this respect. Blood lead levels are significantly different among the studied groups ($p < 0.05$), where the obese gasoline station workers demonstrate highest blood lead levels compared to the other groups, while the healthy obese subjects showed the least value of blood lead levels among the others (Table 1). However, measurements of blood Cd levels did not reveal significant differences among
the three studied groups. Table 2 also indicates that serum visfatin levels in obese subjects with OA were significantly higher than that reported in the other groups, and the obese healthy subjects demonstrate the lowest serum visfatin level compared with others. Finally, Table 2 indicates that TAS values in healthy obese subjects were significantly greater than those reported in the other two groups, which are not significantly different with each other in this regard. In Table 2, serum levels of total cholesterol and LDL-c were significantly elevated in obese OA patients compared with that in other two groups, which showed no significant differences in this regard when compared with each other. Meanwhile, HbA1c and serum levels of TG, HDL-c, and fasting glucose were not significantly different among the three studied groups (Table 2). Correlation studies between blood lead contents and serum visfatin levels indicated that these two parameters were positively and significantly correlated in the three groups, and greatest correlation coefficient value ($r$) was reported in obese OA patients ($r = 0.7, p = 0.02$) followed by healthy obese subject ($r = 0.68, p = 0.005$) and gasoline station workers ($r = 0.54, p = 0.039$), respectively (Figures 1-3). Figure 4 indicates that BMI in obese healthy subjects shows weak positive and non-significant relationship with serum visfatin levels ($r = 0.19, p = 0.49$), while positive and significant correlation ($r = 0.54, p = 0.037$) was reported between these two markers in obese gasoline station workers (Figure 5). However, BMI values and serum visfatin showed weak negative and non-significant correlation ($r = −0.28, p = 0.43$) with serum visfatin levels in obese OA patients (Figure 6).

### Table 1. Body mass index (BMI), blood levels of Cd, Pb, and serum visfatin and total antioxidant capacity (TAS) levels in obese subjects with OA or exposed to heavy metals.

<table>
<thead>
<tr>
<th>Groups</th>
<th>BMI (kg/m²)</th>
<th>Blood Pb (μg/dl)</th>
<th>Blood Cd (μg/dl)</th>
<th>S.Visfatin (ng/ml)</th>
<th>S. TAS (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese + OA ($n = 10$)</td>
<td>35.8 ± 3.5a</td>
<td>19.8 ± 1.6a</td>
<td>0.26 ± 0.03a</td>
<td>53.0 ± 8.2a</td>
<td>0.98 ± 0.15a</td>
</tr>
<tr>
<td>Pb-Exposed ($n = 15$)</td>
<td>32.7 ± 3.4b</td>
<td>23.1 ± 2.2b</td>
<td>0.26 ± 0.04a</td>
<td>42.3 ± 4.7b</td>
<td>1.0 ± 0.27a</td>
</tr>
<tr>
<td>Obese only ($n = 15$)</td>
<td>32.0 ± 2.3b</td>
<td>17.3 ± 2.0b</td>
<td>0.23 ± 0.04a</td>
<td>30.9 ± 3.2a</td>
<td>1.8 ± 0.47b</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD; $n$ = number of subjects; values with non-identical superscripts (a, b, c) for the same parameter within the same group are considered significantly different ($p < 0.05$).

### Table 2. Serum glucose, lipid profile and HbA1c levels in obese subjects with OA or exposed to heavy metals.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cholesterol (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>HDL-c (mg/dl)</th>
<th>LDL-c (mg/dl)</th>
<th>Glucose (mg/dl)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese + OA ($n = 10$)</td>
<td>215 ± 18a</td>
<td>183 ± 13a</td>
<td>48 ± 6a</td>
<td>129 ± 16a</td>
<td>102 ± 8a</td>
<td>6.6 ± 0.5a</td>
</tr>
<tr>
<td>Pb-Exposed ($n = 15$)</td>
<td>198 ± 14b</td>
<td>189 ± 54a</td>
<td>46 ± 7a</td>
<td>114 ± 12b</td>
<td>97 ± 9a</td>
<td>6.4 ± 0.4a</td>
</tr>
<tr>
<td>Obese only ($n = 15$)</td>
<td>193 ± 12b</td>
<td>176 ± 55a</td>
<td>49 ± 7a</td>
<td>109 ± 12b</td>
<td>70 ± 8a</td>
<td>6.3 ± 0.4a</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD; $n$ = number of subjects; values with non-identical superscripts (a, b, c) for the same parameter within the same group are considered significantly different ($p < 0.05$).
4. Discussion

Many reports indicated the involvement of visfatin in obesity and pathogenicity of OA. In the present study serum visfatin was significantly elevated in obese OA patients compared with healthy subjects, and many previous data points to visfatin as a pro-catabolic/pro-inflammatory factor rather than an anabolic factor. Obesity was
considered as one of the risk factors for OA, and characterized by a low-grade inflammatory state that may contribute to harmful effects in many organ systems. The precise metabolic pathways through which obesity contributes to joint structural damage involved aberrant adipokines expression with direct and downstream effects leading to the destruction and remodeling of joint tissue [21] [22], and many cytokines released from adipose tissues may influence OA though direct joint degradation or control of local inflammatory processes [23]. According to the Pearson’s correlation results, the present study does not fully support the hypothesis that adipose tissue is the most important source of circulating visfatin. In this regard Berndt et al. did not show a relationship between plasma visfatin and visceral fat mass assessed by computed tomography scan [24], and macrophages of the adipose tissue can be other major source of visfatin [25]. Gasoline station workers are regularly exposed to many hazardous toxins and noxious substances including heavy metals like Cd and Pb, and can lead to abnormal alterations in the functions of many vital organs. In the present study, the obese gasoline workers showed higher serum Pb levels compared with other obese subjects included in the study. Similar results were obtained in gasoline stations workers within other parts of Iraq [26]. In the present study, the high level of positive correlation between blood lead and visfatin clearly indicates that excessive environmental exposure to lead may predispose to excessive production of visfatin from many tissues. Currently, no study evaluates the relationship between elevated blood lead content and visfatin production, and this might be attributed to the oxidative stress state induced by elevated blood lead levels [27]. In experimental animals, elevated ROS generation damaged the joints matrix and highly correlated with experimentally-induced OA [28], and suppression by Pb of many antioxidant enzymes, including SOD and catalase [29], could be considered as aggravating factor and linked positively with excessive release of visfatin and the apparent decrease in TAS values, reported in the present study, may be
considered as another support for this assumption. The other mechanism by which Pb may contribute to the pathogenesis of OA is through the increase in matrix metalloproteinase 13, associated with elevated cytokines production [30]. The current finding was limited by the small sample size and consequent inability to predict the exact etiology behind the reported changes. Taken together, the reported data in the current study represent a crude finding that need further supported evidence, and further studies highly suggested with larger samples to avoid the limitations of the current work.

5. Conclusion

Serum visfatin levels could be key regulators of obesity and OA, and an important partner with excessive environmental exposure to Pb in the pathogenesis of these disorders.

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Disclosure

No potential conflicts of interest were disclosed.

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