Evaluation Serum Chemerin and Visfatin Levels with Rheumatoid Arthritis: Possible Diagnostic Biomarkers

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a joint-damaging chronic inflammatory disease that affects the synovium and articular cartilage. RA is characterized by symmetric arthritis that primarily affects the tiny joints of the hands and feet. Adipokines play a role in the etiology of a variety of metabolic, vascular, and inflammatory diseases. The goal of this study is to compare the levels of inflammatory adipocytokines (chemerin and visfatin) and their ratios, as well as certain related biomarkers, in RA patients and healthy controls to see if they can help diagnose Rheumatoid Arthritis.

Methods: A total of 70 (25 males and 45 females) RA patients’ group with ages ranging from 45-65 years and 30 (10 males and 20 females) as the control group with ages ranging from 40-70 years old were involved in the study. All individuals had their biochemical parameters, demographic profile and serum chemerin and visfatin concentrations analyzed.

Results: Our findings indicated that serum levels of Visfatin and Chemerin were significantly higher in individuals with rheumatoid arthritis than in healthy controls. Chemerin had moderate positive correlations with C-reactive protein (CRP) and total cholesterol (TC) while, it had weak negative correlation with high-density lipoprotein cholesterol (HDL).

Conclusion: The variations in adipokine levels that we observed could play a role in diagnose of Rheumatoid Arthritis.

Key Words: Rheumatoid arthritis, Chemerin, Visfatin, Adipokines, C-reactive protein, High-density lipoproteins

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting the joints principally. If left untreated, it is the most prevalent inflammatory disease of the joints, characterized by cartilage and bone degradation, leading to functional deterioration and disability. As a result, increasing cartilage and joint degeneration occurs, as well as impairment.1 According to data, women have a 3:1 chance of developing this condition. Any age group can be affected; however, the onset is most common between the ages of 40 and 60.2 Rheumatoid arthritis has no recognized etiology. Clinical signs and symptoms can be caused by a mix of genetic predisposition and environmental triggers. RA is characterized by symmetric arthritis that primarily affects the tiny joints of the hands and feet. General discomfort and swelling of joints (often symmetrically), morning stiffness, and movement limitations that last more than one hour and can be eased by mild motions are all common indications and symptoms of RA.

However, RA can affect any organ, with the most prevalent symptoms being interstitial lung disease, renal amyloidosis, skin vasculitis, episcleritis, and poly-neuropathy of numerous mono-neuropathies. Better diagnostic biomarkers for the early detection of RA are always needed.3 Adipose tissue not only serves as a passive energy storage reservoir, but it also serves as an endocrine gland, producing and secreting a variety of bioactive peptides called adipokines.4 Adipokines play a role in the etiology of a variety of metabolic, vascular, and inflammatory diseases.5 Adiponectin, resistin, leptin, visfatin, plasminogen activator inhibitor type 1 (PAI-1), tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-8 are all adipokines.6 One of the future proteins in inflammatory biomarkers might be chemerin, a 16 kDa protein originally discovered in ovarian cancer patients’ ascitic fluids and synovial exudates from rheumatoid arthritis patients’ synovia as a result of the Tazarotene-induced gene 2 (Tig2).7,8 RA patients have increased
BMI was measured by dividing weight (in Kilograms, Kg) by height squared (in meter, m) for each participant.

Measurement of Body Mass Index: BMI was measured by dividing weight (in Kilograms, Kg) by height squared (in meter, m) for each participant.

RESULTS

Table (1) shows the demographic data of the two studied groups (Rheumatoid arthritis and control). The results obtained from the preliminary analysis shown in table (1) indicated that there was no significant difference in BMI (P = 0.0993) between RA and control groups. There were no significant differences between RA group and the control group regarding age (P=0.5563).

Table (2) shows laboratory data from the blood analysis among the two groups. Our findings indicate there were significant differences between the RA or control groups regarding serum levels of CRP and TC and there were significantly higher in HDL (P< 0.0001) among two groups.

Table (3) shows the different adipokine concentrations among the two groups. Statistical analysis revealed that serum levels of VSF were significantly higher (p< 0.0001) among two groups, as shown in figure (1). Furthermore, serum levels of Chem were significantly higher (P< 0.0001) in RA group compared to controls, as shown in figure (2).

We determined the Pearson’s correlation coefficient among the different variables in the study. There were three significant correlations appeared in RA group. Chemerin had moderate positive correlations with CRP (r=0.452, P=0.031) and TC (r=0.504, P=0.014) while, it had weak negative correlation with HDLc(r=-0.245, P=0.041).

DISCUSSION

Rheumatoid arthritis has been linked in several studies to adipokines. The majority of prior research have focused on pre-existing atherosclerotic diseases or symptoms to narrow down their patient group. In our research, we looked at the serum levels of Visfatin and Chemerin in patients with RA to see what role adipokines have in the disease’s etiology.

In the current study, the RA patients were obese (30.2 ± 3.4), the marked inflammation encountered in them CRP (30.8 ± 3.9) this agreed with Jonssonetal. who reported that RA patients explained this finding by the increase in inflammatory cytokine production.
including rheumatoid arthritis. To examine its significance in the pathophysiology of these disorders, we urged researchers to look at the amounts of the adipokine in serum samples from patients with inflammatory and non-inflammatory rheumatic diseases, as well as healthy controls.13

Serum levels of chemerin is significantly higher (P value<0.0001) in RA patients compared to the healthy individuals, which are similar to findings from a previous study.14 Chemerin was originally recognized in its precursor low biological active state, which was implicated in innate and adaptive immunological responses.15 Once activated, it directed dendritic cells and macrophages to wounded tissues and inflammatory locations, triggering fast defenses throughout the body. Obesity, diabetes, lipid profile components, and early vascular inflammation have all been linked to serum adipokine concentrations.16 Chemerin and its receptor CMKLR1 create a complex that is engaged in immune response modulation and can play a role in the start and resolution of acute inflammation. Increased chemerin levels can promote inflammation by attracting immune system cells. Chemerin also elevated inflammatory mediator expression and production in the affected area. Increased levels of this adipokine in adipose tissue stimulate immune cell recruitment, which leads to increased expression of inflammatory mediators such as CRP, interleukine-6 (IL-6), and tumor necrosis factor alpha (TNF-α), which leads to inflammation exacerbation.17

Many substantial correlations between the measured parameters can be found in the correlation research. Chemerin had a positive correlation with total cholesterol TC (r=0.504, P=0.014) and a negative correlation with HDLc (r=-0.245, P=0.041) in the current study.

Chemerin is thought to regulate lipid metabolism enzymes by lowering cyclic adenosine monophosphate (cAMP) buildup and stimulating calcium release in adipocytes.18 These associations could be related to chemerin’s multiple effects on various biological systems involved in RA disease, which grew stronger as the disease progressed. Chemerin is a protein that affects adipogenesis, angiogenesis, and inflammation,19 and its levels have been found to rise with the duration of RA. Furthermore, serum levels of this adipokine are linked to metabolic syndrome components such as higher BMI and plasma TG level.

In this study, another correlation was found between chemerin with CRP (r=0.452, P=0.031), indicating a relationship with systemic inflammation. This, in part, may be due to the fact that inflammatory cytokines released by adipose tissue stimulate the synthesis of CRP in the liver, which was observed in inflamed tissues, in RA.20

Moreover, serum levels of visfatin were significantly higher (p<0.0001) in RA patients than in the healthy control group, which is in line with observations from previous work of Alkady et al.21 who found that visfatin level was significantly increased in patients with RA.

Visfatin may play a substantial role in the pathophysiology of RA, according to several observations. In certain studies, visfatin was found to be upregulated in active RA in response to proinflammatory stimuli like IL-6. 22 Synovial fluid and serum, the degree of inflammation, the severity of the disease, and joint destruction are all linked to visfatin levels.23 Despite the fact that visfatin is an adipokine, earlier research has found no link between it and obesity. Some research, however, have discovered a link between visfatin and inflammatory markers.24 Visfatin was found in invasive synovial tissue in rheumatoid arthritis patients, and its levels were also elevated in synovial fibroblasts. Visfatin can activate IL6, Matrix metalloproteinase (MMP1 and MMP3), and TNF and IL6 in RA synovial fibroblasts, as well as TNF and IL6 in monocytes.25

**CONCLUSION**

Our findings reveal that chemerin and visfatin levels are significantly higher. Therefore, these alterations in adipokine levels may play a key role in the development of RA-related inflammation.

**ACKNOWLEDGEMENT**

The authors would like to acknowledge staff in Baghdad teaching hospital for their assistance in this work.

**Source of Funding:** No financial assistance was obtained from any sources.

**Conflict of Interest:** The authors declare that they have no known competing financial or personal relationships that could have appeared to influence the work reported in this paper.

**Authors’ Contribution:** This is a collaborative work among all authors.

Author 1: Designing, data collection, data analysis, article writing

Author 2: Data verification, article editing

Author 3: Data collection, article writing

**REFERENCES**

Table 1: Demographic data for the RA and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>RA</th>
<th>P-Value</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(year)</td>
<td>53.39±8.2</td>
<td>54.53±6.9</td>
<td>0.5953</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (Male\Female)</td>
<td>10\20</td>
<td>25\45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>29.6 ± 2.4</td>
<td>30.2 ± 3.4</td>
<td>0.0993</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are shown as mean±SD (Standard Deviation). S: p-value <0.05 (Significant), NS: p-value <0.05 (Non-Significant), HS: p-value <0.0001 (Highly Significant).
Table 2: Clinical and laboratory parameters between the RA and control groups (Mean±SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>RA</th>
<th>P -Value</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg\L)</td>
<td>6.7 ± 1.5</td>
<td>30.8 ± 3.9</td>
<td>0.0042**</td>
<td>S</td>
</tr>
<tr>
<td>TC (mg\dL)</td>
<td>187.9 ± 26.6</td>
<td>170.9 ± 22.3</td>
<td>0.0077**</td>
<td>S</td>
</tr>
<tr>
<td>Triglyceride (mg\dL)</td>
<td>130.7 ± 26.3</td>
<td>128.7 ± 29.2</td>
<td>0.7629</td>
<td>NS</td>
</tr>
<tr>
<td>HDL (mg\dL)</td>
<td>87.9 ± 18.5</td>
<td>54.1 ± 10.7</td>
<td>&lt;0.0001****</td>
<td>HS</td>
</tr>
</tbody>
</table>

CRP – C-reactive protein, HDLc- high-density lipoprotein cholesterol, TC – total cholesterol, TG – triglyceride

Table 3: Comparison of adipokine concentrations among the RA and control groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>RA</th>
<th>P -Value</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemerin (ng\mL)</td>
<td>5.095 ± 1.72</td>
<td>8.887 ± 0.55</td>
<td>&lt;0.0001****</td>
<td>HS</td>
</tr>
<tr>
<td>Visfatin (ng\mL)</td>
<td>0.606 ± 0.23</td>
<td>5.789 ± 2.8</td>
<td>&lt;0.0001****</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 1: Mean Serum VSF in RA and Control.

Figure 2: Mean Serum CHEM in RA and Control.