The Relationship Between the Serum Levels of Resistin and C-Reactive Protein in Egyptian Type 2 Diabetic Patients with and Without Coronary Heart Disease

Safa Refaat (M.D.), Nagwa Abdel Ghaffar Mohamed (M.D.), Hany Abdel Rahman Negm (M.D.) and Khaled Younes (M.D.)

Departments of Internal Medicine and Cardiology, Research Institute of Ophthalmology, Departments of Clinical and Chemical Pathology and Internal Medicine, National Research Center.

Abstract: Insulin resistance is associated with chronic subclinical inflammation. Inflammation has been suggested to play a central role in the development of atherosclerosis. Resistin is expressed primarily in inflammatory cells in humans and has been shown to play a potential role in atherosclerosis. C-reactive protein (CRP) represents one of the acute phase proteins, which increase during systemic inflammation, and previous studies suggested an association between serum resistin levels and serum CRP levels. The aim of this study is to assess the serum resistin level in Egyptian type 2 diabetic patients with and without coronary heart disease, and correlate the resistin level to the level of CRP in those patients. 30 patients with type 2 diabetes mellitus (T2DM) but not coronary heart disease (CHD), 30 patients with T2DM and CHD and 20 subjects matched for age and sex as a control group, participated in this study. Serum resistin was measured using enzyme immunoassay, while serum CRP was measured by rapid latex agglutination procedure. The study revealed an increased serum resistin levels in diabetic patients, either with or without CHD, but the elevation was higher in CHD diabetic patients. The study revealed also a significant correlation of serum resistin to glycosylated hemoglobin (HbA1c), duration of DM, duration of CHD and serum CRP. The relation between serum resistin and DM, CHD and CRP still needs further investigations to be clearer.

Key words: resistin, diabetes mellitus, coronary heart disease and C-reactive protein.

INTRODUCTION

Inflammation has been suggested to play a central role in the development of atherosclerosis. Chronic subclinical inflammation has been identified as an important mechanism in the pathogenesis of type 2 diabetes mellitus (T2DM) and associated cardiovascular complications. The oligocytokine resistin which belongs to a family of cystein-rich C-terminal proteins known as resistin like molecules (RELM; RELMα / FIZZ 1 and RELMB / FIZZ2) of FIZZ (found in inflammatory zone) are thought to be involved in inflammatory processes. Resistin is expressed primarily in inflammatory cells in humans, especially macrophages. Resistin appears to be involved in inflammatory pathways, activate vascular endothelial cells and stimulate smooth muscle cell proliferation, which suggests as a potential role in atherosclerosis.

Resistin mRNA protein has been reported to be present in atherosclerotic lesions. Diabetes is not the only a well known risk factor for atherosclerosis but is also associated with increased levels of sensitive markers of sub clinical systemic inflammation.

Previous studies have highlighted that serum resistin levels are increased in Caucasian T2DM subjects and is associated with changes in C-reactive protein (CRP) levels. CRP represents one of the acute phase proteins, which increase during systemic inflammation. CRP is a known inflammatory marker for T2DM and coronary heart disease (CHD).

The aim of this study is to assess the resistin level in Egyptian type 2 diabetic patients with and without coronary heart disease and correlate the level of resistin to the level of CRP in those patients.

PATIENTS AND METHODS

80 subjects participated in this study, which was approved by the ethical comity. They were classified into 3 groups (A) consisted of 30 patients with type 2 diabetes mellitus with no coronary heart disease, group (B) consisted of 30 patients with type 2 diabetes mellitus and coronary heart disease (diagnosed by previous history of angina pectoris or myocardial infarction or resting ECG ischemic changes in the form of flat or inverted T-wave or depressed S-T segment) and group (C) consisted of 20 apparently healthy
RESULTS AND DISCUSSION

Resistin, a novel adipokine linked to insulin resistance, which is derived mainly from macrophages and identified in atheromas in humans, has been shown to play a potential role in atherosclerosis. Resistin belongs to a novel family of cysteine rich proteins called resistin like molecule or FIZZ, (found in inflammatory zones) proteins[11).

In this study we estimated the serum resistin levels in type 2 diabetic groups of patients not complaining of coronary heart diseases with healthy group and another type 2 diabetic patients complaining of coronary heart diseases and comparing the results. Glycosylated hemoglobin and the inflammatory marker CRP were also estimated for all subjects participated in the study and we correlated to the serum resistin levels of all groups to both.

The study revealed a significant increases in type 2 diabetic patients without CHD and a highly significant increase in the type 2 diabetic groups with CHD. The study revealed also increased levels of CRP in T2DM without CHD, which was more significant in T2DM with CHD.There was a significant correlation of serum resistin to age, male sex, duration of diabetes and glycosylated hemoglobin and a highly significant correlation to CRP and the incidence of CHD.

The results of this study were in accordance to some previous studies and against another some previous studies. Azuma et al 2003 revealed changes in serum resistin to be positively correlated with glucose[12]. Yaun et al 2004[13] demonstrated that plasma resistin concentrations were elevated in patients with type 2 diabetes.

Gustansson and Dgsadl, 2004[14], confirmed that diabetic patients with macro vascular diabetes, as, coronary heart disease, had increased levels of markers of inflammation, but also added new information on a relationship between these markers and glycosylated hemoglobin (HbA, C) indicating an association between degree of glycaemia, inflammation and atherosclerosis.

Reilly et al 2005[14], showed resistin levels to be associated with coronary calcification by computed tomography. Patients with coronary heart disease in their study were found to have higher serum levels of resistin. Ohmori et al 2005[15], reported that serum resistin increased in coronary heart disease patients. Burnett et al 2005[16] reported that resistin was not independently associated with coronary heart disease.

Burnett et al 2006[18] demonstrated that serum resistin concentrations increased in patients with coronary artery disease and they confined also that resistin concentrations were associated with systemic inflammation but they found that plasma concentrations of resistin did not increase in diabetic patients.
Regulate the expression of endothelin-1 (ET-1), functions of vascular cells, activate endothelial cells, up-regulate the expression of endothelin-1 (ET-1), aggravate the proinflammatory response by positive feedback.

Inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor (TNF-α) and IL-12 and hence resistin could also promote production of proinflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor receptor associated factor-3. These proinflammatory mediators have already been implicated in plaque instability responsible of the clinical manifestations coronary artery disease.

The relationship between resistin and insulin resistance, CRP and coronary heart disease still need more investigations to be clearer.

**Conclusion and Recommendation:** Resistin, a novel adipokine which is derived mainly from macrophage, increases in type 2 diabetic patients, especially in those complaining also of coronary heart disease where a significant relation between its serum level and the serum level of C-reactive protein exists, but further investigations concerning these relations are still needed for more confirmation of the results of this study and for explaining these relations.

**REFERENCES**


---

**Table 1:** The clinical and biochemical characteristics of all groups of the study

<table>
<thead>
<tr>
<th>Groups</th>
<th>Parameters</th>
<th>Group (A)</th>
<th>Group (B)</th>
<th>Group (C)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
<td>47.8 ± 1.2</td>
<td>49.2 ± 3.5</td>
<td>50.2 ± 4.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Sex males</td>
<td>17</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>13</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HbA1c (%)</td>
<td>8.2 ± 1.1</td>
<td>9.1 ± 0.6</td>
<td>4.5 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Duration of DM (years)</td>
<td>5.2 ± 2.3</td>
<td>4.9 ± 3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration of CHD (years)</td>
<td>4.1 ± 81.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum resistin (ng/ml)</td>
<td>10.1 ± 1.3</td>
<td>144 ± 3.5</td>
<td>7.6 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Serum CRP (mg/l)</td>
<td>2.9 ± 3.8</td>
<td>5.4 ± 3.3</td>
<td>7.3 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<0.001 Group (A): T2DM, no CHD. Group (B): T2DM and CHD. Group(C): control group.

**Table 2:** the correlation of serum resistin to all other clinical and biochemical parameters of all subjects of the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group (A)</th>
<th>Group (B)</th>
<th>Group(C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Age</td>
<td>0.18</td>
<td>&gt;0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Sex</td>
<td>0.22</td>
<td>&gt;0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.36</td>
<td>&lt;0.05</td>
<td>0.41</td>
</tr>
<tr>
<td>Duration of DM</td>
<td>0.39 &lt;0.05</td>
<td>0.45 &lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Duration of CHD</td>
<td>-</td>
<td>-</td>
<td>0.48 &lt;0.05</td>
</tr>
<tr>
<td>Serum CRP</td>
<td>0.58</td>
<td>&lt;0.05</td>
<td>0.72</td>
</tr>
</tbody>
</table>

P > 0.05: non significant. P < 0.05: significant. P <0.001: highly significant.

---

Al Daghri et al 2005\(^{(17)}\) determined that serum resistin levels were increased in T2DM and CHD in a Saudi population when compared with case control subjects and that a correlation existed between serum resistin and CRP levels in Saudi subjects which suggested a potential role for resistin as a marker associated with inflammation in both T2DM and CHD.

It is possible that the increased plasma resistin concentrations found in diabetic patients are the result of increased production of resistin in adipocytes in hyperglycemic patients and that high glucose concentrations significantly enhance resistin expression\(^{(18)}\). It is possible also that insulin resistance, as occurs during the cause of type 2 diabetes, reflects the diminished ability of insulin to suppress resistin expression by adipocytes\(^{(19)}\).

Patients with coronary artery disease usually have coronary plaques with was extensive macrophages rich areas, which are the major sources of resistin\(^{(20)}\). Inflammatory responses stimulated resistin secretion and resistin could also promote production of pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and IL-12 and hence aggravate the proinflammatory response by positive feedback\(^{(9)}\).

On the other hand, resistin could also affect functions of vascular cells, activate endothelial cells, up-regulate the expression of endothelin-1 (ET-1), adhesion molecules and chemokines, induce marked metalloproteinases expression, increase CD40 ligand signaling by down regulation of tumor necrosis factor receptor associated factor-3. These proinflammatory mediators have already been implicated in plaque instability responsible of the clinical manifestations coronary artery disease\(^{(21)}\).

The relationship between resistin and insulin resistance, CRP and coronary heart disease still need more investigations to be clearer.


