Original Research Article

Study The Relationship of IL-33 with Adiponectin in Postmenopausal Female with and without Type 2 Diabetes Mellitus

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Abstract

Postmenopausal women influence by several physiological changes such as coronary artery disease, obesity and insulin resistance. Interleukin-33 (IL-33) a cytokine which have a protective effect to cardiovascular disorders and regarded either pro- or anti-inflammatory. Adiponectin is a hormone with anti-inflammatory properties, associated with hyperlipidemia and insulin resistance. The aim of this study is to investigate the relationships of IL-33, adiponectin with atherogenicity as considered risk factor for heart disease in postmenopausal women with and without type 2 diabetes mellitus.

Ninety women age between (54-62) years were enrolled in this study. Fasting blood glucose (FBG), glycated hemoglobin (HbA1c), body mass index (BMI), lipid profile, atherogenic index of plasma (AIP), IL-33 and adiponectin levels were determined in patients and control groups.

The results revealed highly significant increase in FBG, HbA1c, BMI, TC, TG, LDL-c, VLDL-c and AIP. While reduce HDL-c, adiponectin and IL-33 levels were founded in postmenopausal women when comparing to control group. Furthermore, a positive correlation was observed in IL-33 with HbA1c, also with AIP, but a negative significant correlation between IL-33 and adiponectin, also between IL-33 and BMI in diabetic postmenopausal women group. Conclusion from the results of present work lead to suggest that higher reduction in IL-33 and adiponectin levels in diabetic postmenopausal women may be useful in predict action of cardiovascular disorders.

Key words: Interleukin-33, Adiponectin, postmenopausal, atherogenicity.

دراسة علاقة مستويات الانترلوكين-33 مع الاديبونكتين لدى نساء سن اليأس من المصابات وغير المصابات بدء السكري من النوع الثاني

الخلاصة

أن النساء في مرحلة سن اليأس يتعرضن للإصابة بإمراض القلب والسمنة إضافة للحساسية تجاه الأنسولين نتيجة لتأثير مجموعة من التغييرات الفسيولوجية التي تحدث في هذه المرحلة. الإنترلوكين-33 ينتمي لعائلة الإنترلوكين-1 ويعتبر كدالة تنوبية لأنواع متعددة من أمراض القلب. أما الاديبونكتين فهو هرمون بروتيني يمتلك خصائص مضادة لالتهاب وخصوصا تلك المتعلقة بإرتفاع نسبة الدهون والحساسية تجاه الأنسولين.

ان هدف الدراسة الحالية هو إيجاد العلاقة بين مستويات الإنترلوكين-33، الاديبونكتين ومؤشر البلازما المعصم بأعتبارهم عامل ظروفة للإصابة بأمراض القلب لدى نساء سن اليأس من المصابات وغير المصابات بدء السكري من النوع الثاني.
Introduction

Menopause is a natural distinguish of the reproductive years end with cessation of cyclic ovarian functions which manifested by cyclic menstruation [1]. Menopause is associated with elevation in follicle-stimulating hormone and luteinizing hormone levels with a decrease in estrogens [2]. The levels of hormones show a significant effect on the metabolism of lipids and lipoproteins [3]. Antiatherogenic effect of estrogen and the protection of females against heart disease are signifies during the premenopausal period [4]. Several physiological changes that develop during menopause may prone to the risk of cardiovascular disease (CVD), increase obesity or low metabolic rate resting and physical activity [5]. During premenopausal period insulin resistance become more prevalent and many women have increasing in blood sugar levels, due to sex hormones effect, also when women reach menopause the body becomes more sensitivities to insulin like it was prior to premenopausal period [6].

Interlukin-33 (IL-33) is a cytokine related to IL-1 super family [7]. IL-33 is a protein which has a role in signaling damage of the cell pathogenesis of the inflammatory disease by releasing from necrotic or damaged cell [8]. Other research demonstrated that IL-33 is distributed throughout different organ systems in the body, which expressed in non hematopoietic cell, including fibroblasts, adipocytes, smooth muscle cell, endothelial and intestinal epithelial cells [9]. IL-33 has been demonstrated to have a potent protective role in various experimental chronic heart failure studies through inhibition of the nuclear factor kappa B cascade. So that, IL-33 plays a role in various cardiovascular disorders [10]. IL-33 could act earlier in artery inflammatory cells and modulate the innate immune responses by regulation macrophage effector function [11]. From the other side, IL-33 has protected effect against atherosclerosis, obesity and type2 diabetes (T2D). Therefore, IL-33 considered pro- or anti-inflammatory based on the model of disease [12].

Adiponectin is a novel collagen like protein synthesized by adipocytes and acts as a hormone with anti-inflammatory and insulin sensitizing properties through decrease the risks of T2D, including suppression of hepatic gluconeogenesis, or stimulation of fatty acid oxidation in the liver and glucose uptake in skeletal muscle [13]. Adiponectin which have antiatherogenic properties [14] and inversely associated to hyperlipidemia and insulin resistance [15]. Adiponectin enhances glucose utilization and the oxidation of fatty acid in muscle. Also increase endothelial nitric oxide secretion, inhibits monocyte adhesion and smooth muscle cell proliferation in the vascular wall [16].

Data in IL-33 levels and correlate it with adiponectin in menopausal women with and
without T2DM are not available. So that from this point the present research aimed to investigated the association between the IL-33 levels, adiponectin and atherogenicity as consideration risk factor for CVD in postmenopausal women with and without T2DM.

**Materials and Methods**

Ninety women age ranged between (54-62) years were selected from those attending to Baghdad Teaching Hospital from October 2013 to March 2014. They were recruited as 50 postmenopausal women with T2DM and 40 apparently healthy postmenopausal women as control group. Menopause was confirmed by the absence of menstruation for more than two years [17]. Exclusion criteria consisted of those haring a history of menstrual disorders, thyroid abnormalities, inflammatory or infection disease, autoimmune and rheumatic’s disease, fever, cancer as well as those who under treatment with steroidal anti-inflammatory drugs were excluded. BMI was measured based on world Health Organization (WHO) procedure [18].

Fasting blood samples from all subjects were collected to analyzed glycated hemoglobin (HbA1c) [19], fasting blood sugar [20], total cholesterol [21], triglyceride [22], HDL-c [23]. AIP was estimated: log TG/HDL-c [24] in both groups. Serum IL-33 and adiponectin levels were measured by an enzyme immuno assay (ELISA) [25].

**Statistical Analysis**

Student T-test was used to compare the significance of the difference in the mean values of two groups. The results were expressed as mean ± SD. The P-value ≤0.05 was considered significant. Pearson coefficient (r) was applied to describe the relation between the different studied variables P-value <0.0001 was considered significant.

**Results**

Table (1) shows the mean of age, BMI, HbA1c, FBG, TCh, TG, HDL-c, LDL-c, VLDL-c, AIP, adiponectin and IL-33 levels in diabetic postmenopausal group and control group. The results showed a highly significant elevation in BMI level, HbA1c, FBG, TCh, TG, LDL-c, VLDL-c and AIP in diabetic postmenopausal group comparing to control group. Also a high significant reduction was observed in the levels of LDL-c, adiponectin and IL-33 in patient group than control group.
Table 1: Descriptive characteristic of parameters in patients and control groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group</th>
<th>Patients group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>55±6.1</td>
<td>56±4.2</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.13±1.20</td>
<td>33.21±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>4.57±1.43</td>
<td>9.13±1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>91.27±13.09</td>
<td>283.53±92.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCh (mg/dl)</td>
<td>180.93±16.86</td>
<td>229.40±10.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>91.50±6.95</td>
<td>145.50±112.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-c (mg/dl)</td>
<td>42.80±4.78</td>
<td>28.97±4.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-c (mg/dl)</td>
<td>119.90±17.04</td>
<td>194.67±18.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL-c (mg/dl)</td>
<td>18.6±1.39</td>
<td>60.87±32.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIP</td>
<td>0.33±0.07</td>
<td>0.94±0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>10.49±1.46</td>
<td>4.64±0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-33 (pg/ml)</td>
<td>25.29±1.31</td>
<td>18.21±1.71</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data in table (2) indicate presence a correlation in IL-33 with HbA1c, BMI, adiponectin and AIP in diabetic postmenopausal women. A highly significant positive correlation was observed in IL-33 levels with HbA1c (r =0.165, P<0.001) and with AIP (r=0.632, P<0.001) in diabetic postmenopausal women but, a negative significant correlation was founded in IL-33 with adiponectin (r= -0.791, P<0.001) and BMI (r = -0.815, P<0.001).

Table 2: Correlation of IL-33 with HbA1c, AIP, adiponectin and BMI.

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-33 &amp; HbA1c</td>
<td>0.165</td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>&lt;0.001</td>
</tr>
<tr>
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</tr>
<tr>
<td>IL-33 &amp; BMI</td>
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<td>&lt;0.001</td>
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Discussion

The results in the present investigation showed significant elevation in levels of HbA1c, FBG, TCh, TG, LDL-c, VLDL-c and AIP in diabetic postmenopausal women compared with that in participants without diabetic, which agreement with other studies [26] [27] [28]. Probably, that related to the changes in hormones and follicular failure development in these ages. AIP has been used a risk factors for CVD [29], to based on our findings diabetic and non diabetic postmenopausal women at a high risk of developing cardiovascular disease [30]. The mean value of BMI was significantly higher in diabetic postmenopausal women when compared with control group and that agree with previously demonstrated [31]. Hyperglycemia associated with increase protein glycation which led to the high levels of HbA1c are commonly in this situation and that responsible for many chronic complication such as increase in body weight, dyslipdemia and increase the risk for atherosclerosis [32].

This study also, showed that the serum adiponectin levels in patients group were lower than levels of control group significantly. Adiponectin secreted by adipocytes and act as hormone contribute in homeostatic control of glucose and lipid
levels so that in T2DM patients adiponectin levels well reduce [33]. Hypoadiponect-enemia has many adverse clinical consequences as adiponectin has antiatherogenic and anti-inflammatory properties [34]. Al-Zubadi et al suggested that adiponectin may have important role in the CVD pathogenesis in both gender with T2DM [35]. Low concentration of adiponectin associated with atherosclerosis development which led to anti-inflammatory effect of adiponectin as protective agent against atherogenic vascular change [36, 37]. So that, adiponectin becomes benefic in the prevention of.

Serum IL-33 levels in diabetic postmenopausal women were significant decrease than those non-diabetic postmenopausal women. In patients group there was a highly significant positive correlation in IL-33 with HbA1c and AIP were founded. Also, there was a highly significant negative correlation was observed in IL-33 with BMI and adiponectin level. No such correlation existed between IL-33 and HbA1c, AIP, BMI and adiponectin in diabetic postmenopausal women. IL-33 play important role in many heart disorders. The reduction in IL-33 levels in diabetic mellitus patients may due to the protective effect of IL-33 by reducing adiposity and improving glucose tolerance and insulin resistance [38]. To our knowledge, this is the first study that high lights on levels of IL-33 and related with adiponectin concentration in menopausal women with and without diabetic mellitus. Therefore, the finding of the present work lead to suggest that higher reduction in IL-33 and adiponectin levels in diabetic postmenopausal women may be useful in predict action of cardiovascular disorders.

References
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