Comparative Biochemical Study of Insulin like Growth Factor-1(IGF-1) in Sera of Controlled and Uncontrolled Dyslipidemia in Type2 Diabetic Iraqi Patients and Healthy Control.

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Received in: 1/June/2015, Accepted in:30/June/2015

Abstract

The objective of the present study is to compare the effect of insulin like growth factor-1 on the lipid profile in sera of diabetic patients with and without dyslipidemia having the same medical treatment and compared with healthy control. The study included three groups. The biochemical parameters which were measured include, fasting blood sugar(FBS), glycated hemoglobin (HbA1c), fasting insulin, insulin like growth factor -1(IGF-1), lipid profile [Total cholesterol (Tc) , triglyceride(TG), high density lipoprotein cholesterol(HDL-c) ,low density lipoprotein-cholesterol (LDL-c)and very low density lipoprotein-cholesterol (VLDL-c)], Atherogenic index of plasma(AIP), insulin resistance(IR). The results revealed a significant increase in FBS, HbA1c, Tc, TG, LDL-c, VLDL-c, AIP, insulin level and HOMA-IR while a significant decrease in IGF-1 and HDL-c in G2 and G3 was noticed comparing to G1. The conclusion could be drown from the present study that low levels of IGF-1 in groups comparing with healthy control, which may be led to the high levels of insulin resistance, while no effect of dyslipidemia on IGF-1.

Key words: Type2 diabetes mellitus DM, IGF-1, IR.
Introduction

Insulin-like growth factor-1 (IGF-1) is a small polypeptide (70 amino acid & 7500 KDa) straight chain synthesized mainly by the liver in response to growth hormone (GH) action [1]. It shares nearly 50% amino acid sequence homology with proinsulin, it composed of an alpha and a beta chain connected by disulfide bonds [2]. IGF-1 is present in circulation in the free form and in the form complexed with protein which bind (IGFBP). Six IGF-binding proteins were identified with various affinity to IGF-1, main binding protein of IGFs is IGFBP-3 and its synthesis is mainly determined by growth hormone [3]. IGF-1 synthesis remains linked to nutrient intake and has retained some insulin-like properties such as stimulation of glucose transport into skeletal muscle cell [3]. Decreased levels of circulating IGF-1 in diabetic patients have been discovered to be associated with insulin resistance [4], which is a pathological state in which insulin action is impaired in target tissues, including liver, skeletal muscle and adipose tissue [5].

IGF-1 levels are strongly determined by changes in growth hormone secretion [6]. Dyslipidemia is increased in the lipid and lipoprotein, it is elevated of plasma cholesterol (TC), triglyceride (TG), or both, or a low HDL-c level that contributes to the development of atherosclerosis [7]. The abnormal lipid profile observed in type 2 DM may be related to insulin resistance which has been closely associated with diabetic dyslipidemia and hypertension [8,9].

Aim of the study

The aim of this study is to compare the effect of insulin like growth factor-1 on the lipid profile in sera of Iraqi diabetic patients with and without dyslipidemia having the same medical treatment and compared with healthy control, this may provide an additional factor of glucose homeostasis.

Subjects and methods

The studied groups comprised of (20) subjects [(10) male and (10) female] as healthy control group 1 (G1) and G2 which consist of type 2 DM with controlled lipidemia [(11) male and (9) female] and G3 which consist of type 2 DM patient with dyslipidemia [(9) male and (11) female]. All studied groups matched with age range (45-65) years and body mass index (BMI) (25-29 Kg/m²). Smokers, alcoholics and patient with cardiovascular disease, insulin treatment, kidney disease, hepatic failure and statins treatment were excluded.

Blood samples were collected from venipuncture each subject in the study after 12 hours fasting. Samples were immediately centrifuged and serum was separated and frozen until assayed, for determination of fasting serum glucose [10]. Total cholesterol [11], high density lipoprotein cholesterol HDL-c [12] and triglyceride TG [13] were determined by using commercial kits (Bio Labo SA-France). LDL-c and VLDL-c were calculated by Freidweild equation [14].

\[
LDL-c = \text{Total cholesterol} - (\text{HDL-c} + \text{VLDL-c})
\]

\[
\text{VLDL-c (mg/dL)} = \left(\frac{\text{TG (mg/dL)}}{5}\right)
\]

Fasting serum insulin [15] was determined by using ELISA kit (DRG-GERMANY). Insulin like growth factor-1 (IGF-1) was determined by radioimmunoassay using commercial kits (Beckman Coulter )-Germany. The bound radioactivity is directly proportional to IGF-1 concentration in the sample (IMMUNOTECH s.r.o – Radiova , I ). Insulin resistance was assayed by calculating the homeostasis model assessment for insulin resistance (HOMA-IR) which is estimated using the following formula.

\[
\text{HOMA-IR} = \left[\frac{(\text{Fasting glucose} \times \text{Fasting insulin})}{405}\right]
\] [16].
Atherogenic index of plasma (AIP) calculated from the formula \(\text{AIP} = \log(\text{TG}/\text{HDL-c})\) [17]. The results were expressed as mean ± SEM and \(P \geq 0.05\) was considered significant. Unpaired student t-test was used to examine the differences of mean.

**Results and discussion**

Table (1) showed a significant increase in fasting blood sugar (FBS) in both diabetic groups, \(G_2 (167.45 ± 7.66 \text{ mg/dL})\) and \(G_3 (201.75 ± 15.14 \text{ mg/dL})\) compared to control group \((86.5 ± 2.06 \text{ mg/dL})\), no significant elevation between \(G_2\) and \(G_3\) was observed. Patients with type 2 DM characterized by insufficient secretion of insulin as a defect of islet cell function or \(\beta\)-cell mass which cause an increase in blood sugar[18]. Glycated hemoglobin (HbA1c) showed a significant increase in both diabetic groups, \(G_2 (7.84 ± 0.22\%)\) and \(G_3 (8.40 ± 0.42\%)\) compared with \(G_1 (5.74 ± 0.09\%).\) A significant correlation was found between \(G_1\) comparing to \(G_2\) and \(G_3\), while no significant correlation between two diabetic groups was found. It has been reported that the prevalence and overlap between intermediate hyperglycemia was defined by HbA1c\((5.7-6.4\%)\), this range was proposed as an indicator of type 2 DM.

Table (2) showed the levels of lipid profile and AIP in all studied groups. No significant elevation was found in \(T_c, \text{TG, LDL-c, VLDL-c and AIP}\) in \(G_2\) comparing to \(G_1\) which \(T_c(169.25 ± 6.47 \text{ mg/dL})\) comparing to \(G_1(168.75 ± 4.12 \text{ mg/dL})\) and \(\text{TG}(138.85 ± 3.11 \text{ mg/dL})\) comparing to \(G_1(127.33 ± 3.59 \text{ mg/dL})\), \(\text{LDL-c} (89.85 ± 3.31 \text{ mg/dL})\) comparing to \(G_1(88.75 ± 3.92 \text{ mg/dL})\), \(\text{VLDL-c} (27.77 ± 0.91 \text{ mg/dL})\) comparing to \(G_1(26.15 ± 1.21 \text{ mg/dL})\) and \(\text{AIP} (0.45 ± 0.02)\) comparing to \(G_1(0.36 ± 0.02)\). The results also revealed significant reduction in \(\text{HDL-c levels in } G_2(44.95 ± 1.61 \text{ mg/dL})\) comparing to \(G_1(54.65 ± 1.08 \text{ mg/dL})\).

A significant increase in \(T_c, \text{TG, LDL-c, VLDL-c and AIP}\) in \(G_3\) was found comparing to \(G_2\) and \(G_1\) which \(T_c(192.7 ± 12.35 \text{ mg/dL})\) was \(G_1(168.75 ± 4.12 \text{ mg/dL})\) and \(\text{TG}(186.75 ± 16.44 \text{ mg/dL})\) was \(G_1(138.85 ± 3.11 \text{ mg/dL})\). A significant increase in \(\text{HDL-c}\) was noticed in \(G_3\) \((44.1 ± 1.80)\) comparing to \(G_1\), while no significant reduction was found between \(G_2\) and \(G_3\). The data in present study showed that dyslipidemic subject had two lipid values outside the normal range of which the most frequent combination was low \(\text{HDL-c}\) and high \(\text{LDL-c}\) which is in agreement with Cook et al study[19] who observed that 54% of DM subjects had two lipid values reduced \(\text{HDL-c}\) and increased \(\text{LDL-c}\) as the most frequent combination outside the normal range. The most lipid abnormality in our study reduced \(\text{HDL-c}\) which is in agreement with Okafo et al study[20]. Previous study revealed that insulin resistance may be responsible for low \(\text{HDL-c}\) in patient with type 2 DM[21]. The production of \(\text{HDL-c}\) decreases due to the alteration in hepatic function and increased activity of hepatic lipase which facilitates \(\text{HDL-c}\) clearance. Dyslipidemia is elevation of plasma cholesterol, triglycerides, or both or a low \(\text{HDL-c}\), that contributes to the development of atherosclerosis [22]. Our study revealed that there is a slightly increase in \(\text{AIP}\) in \(G_2\) who controlled their lipidemia and high increase of \(\text{AIP}\) in \(G_3\) with dyslipidemia comparing with control \((0.45 ± 0.02)(0.6 ± 0.04)\) respectively with \((0.36 ± 0.01)\), which is in agreement with Hermans et al study[23]. The highest value of \(\text{AIP}\) increased significantly with increased atherogenic risk \((0.2-0.5)\) and in patients with diabetes AIP value was among the highest level[24], therefore, AIP is considered a higher predicted value for atherosclerosis[25]. A study data of AIP value revealed the increasing of AIP value proportion to the cardiovascular (CV) risk, this value increased up to (0.4), the data showed the AIP (0.1-0.24) with medium risk and above (0.24) with high CV risk [26].

Results in table (3) indicate that serum levels of \(\text{IGF-1(ng/ml)}\) in \(G_2\&G_3\) (104±6.77 ng/ml) , (116.9±9.19 ng/ml) respectively were significantly decreased, compared with \(G_1\) (236.45 ± 8.93 ng/ml).
Serum IGF-1 levels in patients with type 2 diabetes depend on the degree of metabolic control, with near normal IGF-1 levels in well controlled diabetics and decreased in poorly controlled diabetics, it has been suggested that lowered serum IGF-1 concentration predict worsening of insulin-mediated glucose uptake in older people[27]. Conti et al[28] reported that insulin has a profound influence on the IGF-1 axis and variation circulating insulin concentration is an important determination of IGF-1 bioactivity, that means the fasting decreases insulin levels which then reduces the concentration of growth hormone (GH) receptors in hepatocytes which in turn causes a reduction in IGF-1. Hasan et al[29] indicated that IGF-1 can be useful marker in the insulin resistance because low IGF-1 level can help as a better identification of subject at risk type diabetes and cardiovascular disease.

The data in table (3) showed a significant reduction of IGF-1 in G2 and G3 comparing to G1. No significant reduction was observed between two diabetics groups G2&G3. Also the results presented in table-3 indicated that fasting insulin and HOMA-IR values were significantly higher in G2&G3 than healthy control subjects. Insulin levels for G2&G3 was (15.79±1.45ng/ml) (17.46±1.09ng/ml) respectively compared with G1(2.32±1.11ng/ml). No significant elevation between G2&G3 was noticed. Homeostasis insulin resistance (HOMA-IR) was significantly increased in G2&G3(6.67±0.70)(8.58±0.79) respectively compared with G1(2.7±0.28). No significant elevation between G2&G3 was noticed.

Dyslipidemia and insulin resistance are both considered to be risk factors for metabolic syndrome, insulin resistance are associated with low IGF-1 level, depression of HDL-c concomitant with elevation of LDL-c, increasing risk of obesity and type 2 diabetes[30]. Low IGF-1 level was found in diabetic patients which have been discovered to be associated with insulin resistance[4]. The action of IGF-1 is directly on the balance between GH and insulin to the control of glucose homeostasis [31].

Conclusions

The results of the present study indicate that there is no effect of dyslipidemia on IGF-1 level which there are no significant reduction found between controlled and uncontrolled dyslipidemia diabetic patients.

References

9. Mgonda, YM.; Ramaiya, KI.; Swai, ABM.; McLarity, DG.; and Albert, KGM. (1998). Hypertension; 31:114-118.


Table (1): Descriptive parameters of the studied groups.

<table>
<thead>
<tr>
<th>Groups parameters</th>
<th>G₁ Mean ± SEM</th>
<th>G₂ Mean ± SEM</th>
<th>G₃ Mean ± SEM</th>
<th>G₁&amp;G₂ T. test</th>
<th>G₁&amp;G₃ T. test</th>
<th>G₂&amp;G₃ T. test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject.NO</td>
<td>Male (10)</td>
<td>Male (11)</td>
<td>Male (9)</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Female (10)</td>
<td>Female (9)</td>
<td>Female (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBS(mg/dL)</td>
<td>86.5±2.06</td>
<td>167.45±7.66</td>
<td>201.75±15.14</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.74±0.09</td>
<td>7.84±0.22</td>
<td>8.40±0.42</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table (2): Levels of lipid profile and AIP in all studied groups.

<table>
<thead>
<tr>
<th>Groups parameters</th>
<th>G1 Mean ± SEM</th>
<th>G2 Mean ± SEM</th>
<th>G3 Mean ± SEM</th>
<th>G1&amp;G2 T. test</th>
<th>G1&amp;G3 T. test</th>
<th>G2&amp;G3 T. test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc (mg/dL)</td>
<td>168.75±4.12</td>
<td>169.25±6.47</td>
<td>192.7±12.35</td>
<td>NS</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>127.3±3.59</td>
<td>138.85±3.11</td>
<td>186.75±16.44</td>
<td>NS</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>54.65±1.08</td>
<td>44.95±1.61</td>
<td>44.1±1.80</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>88.75±3.92</td>
<td>89.85±6.31</td>
<td>113.45±13.77</td>
<td>NS</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>VLDL-c (mg/dL)</td>
<td>26.15±1.21</td>
<td>27.77±0.91</td>
<td>36.9±3.32</td>
<td>NS</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>AIP</td>
<td>0.36±0.02</td>
<td>0.45±0.02</td>
<td>0.60±0.04</td>
<td>NS</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Table (3): Levels of IGF-1, insulin, HOMA-IR in all studied groups.

<table>
<thead>
<tr>
<th>Groups parameters</th>
<th>G1 Mean ± SEM</th>
<th>G2 Mean±SEM</th>
<th>G3 Mean±SEM</th>
<th>G1&amp;G2 T. test</th>
<th>G1&amp;G3 T. test</th>
<th>G2&amp;G3 T. Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>236.45±8.93</td>
<td>104.4 ±6.77</td>
<td>116.9±9.19</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin Level (ng/ml)</td>
<td>2.32±1.11</td>
<td>15.79±1.45</td>
<td>17.46±1.09</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.7±0.28</td>
<td>6.67±0.70</td>
<td>8.58±0.75</td>
<td>S</td>
<td>S</td>
<td>NS</td>
</tr>
</tbody>
</table>
دراسة مقارنة المتغيرات الكيميائية لعامل النمو شبيه الإنسولين-1 في إمصال المسيطرين وغير المسيطرين على الدهون في مرضى النوع الثاني للسكري العراقيين مع الأصحاء.

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الخلاصة
تهدف الدراسة الحالية إلى مقارنة تأثير عامل النمو شبيه الإنسولين-1 على صورة الدهون في إمصال مرضى مرض السكري المسيطرين وغير المسيطرين على ارتفاع الدهون بالدم الذين تم قياسهما للمعالجة الطبية نفسها ومقارنتهم مع الأصحاء.
وتضمنت المتغيرات الكيميائية التي تم قياسها سكر الدم، الدهون الكلية، الدهون الكبدية، الدهون الثلاثية، الكوليسترول، الكوليسترول HDL، الكوليسترول LDL، الفازورين، الكوليسترول الكلي، الدهون الثلاثية، السيتوكينات، إلخ. كانت النتائج عن زيادة معنوية في الكولسترول، الكوليسترول HDL، الكوليسترول LDL، الدهون الثلاثية، الفازورين، إلخ.
بينما لوحظ نقص معنوي في عامل النمو شبيه الإنسولين-1 والكوليسترول LDLC و觎الة الكالسيوم في المجموعة 2 والجموعة 3، بالمقارنة مع المجموعة 1. المحصلة التي استنجدت من هذه الدراسة أن انخفاض عامل النمو شبيه الإنسولين-1 في المجموعة بمقارنة مع مجموعة الأصحاء قد يؤدي إلى مصطلحات عالية من مقاومة الإنسولين بينما لا يوجد تأثير لارتفاع الدهون في الدم على عامل النمو شبيه الإنسولين-1.

الكلمات المفتاحية: داء السكري النوع الثاني، عامل النمو شبيه الإنسولين-1، مقاومة النسولين.