Correlation between Uric Acid and Liptin with Its Ratio in a Sample of Iraqi Patients with Diabetes Mellitus

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Abstract
In this study the relation between uric acid and leptin hormone with its ratio, was investigated among sample of Iraqi diabetic patients. A case control study conducted in the National Diabetes Center, College of Medicine at Al-Mustansiryia University in Baghdad-Iraq. Hemoglobin A1c (HbA1c), fasting blood sugar, leptin and uric acid were measured. One hundred forty patients with DM was inhered in this study, and 100 subjects were healthy as a control revealed a highly significant increasing in serum (FBS), HbA1c, body mass index (BMI), Leptin and uric acid of diabetes patients than in healthy subjects( p < 0.0001). While the ratio of glucose /leptin of diabetes patients was highly significant decrease compare to healthy subjects. As well as the present study indicate a positive relation between serum uric acid with HbA1c of diabetes mellitus patients and uric acid with leptin diabetes mellitus patients ((p < 0.0001).

Keywords: Diabetes mellitus, Leptin, Uric acid, Glucose/leptin.

Introduction
Uric acid is the final oxidation product of purine catabolism. Serum uric acid is positively associated with serum glucose in healthy subjects.[1-7] However, this association is not consistent between healthy and diabetic individuals [8–10], as a low serum level of uric acid is reported in the hyperglycemic state [11].Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes [12,13].

The association of high serum uric acid with insulin resistance has been known since the early part of the 20th century, nevertheless, recognition of high serum uric acid as a risk factor for diabetes has been a matter of debate. In fact, hyperuricemia has always been presumed to be a consequence of insulin resistance rather than its precursor [14-18]. However, it was shown in a prospective follow-up study that high serum uric acid is associated with higher risk of type 2 diabetes independent of obesity, dyslipidemia, and hypertension [19].Leptin is a peptide hormone encoded by the obesity gene. It is a 16-KDa food intake, reproduction, and immune function, plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. It is one of the most important adipose derived hormones [20, 21].

Human leptin is a protein of 167 amino acids. It is manufactured primarily in the adipocytes of white adipose tissue, the major source of leptin, it can also be produced by brown adipose tissue, placenta, ovaries, skeletal muscle, stomach, mammary epithelial cell, bone marrow and liver [22]. The absence of leptin (or its receptor) leads to uncontrolled food intake and resulting obesity. Several studies have shown that fasting or following a very low calorie diet (VLCD) lowers leptin levels [23].It might be that on short-term leptin is an indicator of energy balance. This system is more sensitive to starvation than to overfeeding; leptin levels change more when food intake decreases than when it increases [24]. It might be that the dynamics of leptin due to an acute change in energy balance are related to appetite and eventually to food intake. Although this is a new hypothesis, there are already some data that support it [25, 26].

The finding of a positive correlation between serum leptin and uric acid levels suggests that leptin could be a pathogenic factor responsible for hyperuricemia in obesity [27].

Material and Method
A case-control study was conducted during the period from 1st August 2008 to the 25th of May 2010, in the National Diabetes Center,
College of Medicine at Al-Mustansirya University in Baghdad Iraq. One hundred forty patients with diabetes mellitus (DM), male=52, female=88, type 1=74 and type 2=99, were enrolled in this study. Their age range was 30-55 years. None of that patient had cardiovascular diseases (CVD), liver disease, and renal failure. A 100 healthy non-diabetic subject were used as a control, 32 were males and 68 were females with the age rang from 30-55. Serum glucose was measured at biochemistry Laboratory at College of Science/chemistry Department at Al-Nahrain University from a fasting sample of participants 8-12 hr by enzymatic colorimetric method (GOD-PAP). Serum uric acid was measured at the Biochemistry Laboratory at National Diabetes Center by enzymatic colorimetric method (Linear). HbA1c was measured by column chromatography method (Varna-Biurat /HPLC). Serum leptin was measured using high performance Liquid Chromatography (HPLC), Shimadzu (Kyoto, Japan) which consisted of a system controller model SCL-10 AVP, a degasser model DGU-12A, two liquid delivery pumps model LC-8 AVP, UV-Visible detector model SPD-10AVP, and injector model SIL-10A, equipped with 20 µl sample loop. The HPLC system has been interfaced with computer via a Shimadzu class-VP5 chromatography data system program supplied by the manufacturer, Épson LQ-300 printer model P852A (Japan).

All samples and standard solution have been chromatographically analyzed with ODS column using gradient mobile phase 30% acetonitrile, 70% estimate water, flow rate 1 ml/min and UV-VIS detection at wavelength 233 nm in order to estimate serum leptin[28]. Normal reference ranges for leptin were [7.36±3.73 ng/ml] according to American Medical Association [29]. Body mass index was calculated by dividing study subject weight (kg with their height (m²) [30].

All data were analyzed by SPSS version 17. Descriptive statistics in terms of mean and Standard Deviation calculated for patients and healthy control. Pearson’s correlation as well as linear regression equation was calculated to estimate the slope (B) in order to know the amount of change in dependent variables with per unit change in serum selenium concentration. A P-value of <0.05 was considered as significant.
Table (1)

<table>
<thead>
<tr>
<th></th>
<th>General (n=140)</th>
<th>Male (n=52)</th>
<th>Female (n=88)</th>
<th>Type I (n=74)</th>
<th>Type II (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.63±6.11</td>
<td>45.54±4.59</td>
<td>45.68±6.90</td>
<td>44.59±6.95</td>
<td>46.63±4.85</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>171.91±62.92</td>
<td>187.86±77.43</td>
<td>154.03±34.22</td>
<td>187.86±77.43</td>
<td>154.03±34.22</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.65±2.18</td>
<td>8.664±1.90</td>
<td>8.64±2.34</td>
<td>9.15±2.28</td>
<td>8.09±1.93</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.88±4.87</td>
<td>26.72±3.22</td>
<td>26.98±5.65</td>
<td>27.45±2.92</td>
<td>26.25±6.38</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>22.86±5.81</td>
<td>23.27±5.21</td>
<td>24.61±6.19</td>
<td>23.73±6.318</td>
<td>21.87±5.11</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.86±1.73</td>
<td>6.06±1.60</td>
<td>5.74±1.81</td>
<td>6.32±1.76</td>
<td>5.35±1.57</td>
</tr>
<tr>
<td>Glucose/leptin ratio</td>
<td>7.85±3.06</td>
<td>7.69±3.08</td>
<td>7.95±3.09</td>
<td>8.08±3.09</td>
<td>7.59±3.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Healthy control (n=100)</th>
<th>(n=32)</th>
<th>(n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.41±5.72</td>
<td>45.21±5.52</td>
<td>45.81±5.48</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>86.58±4.22</td>
<td>87.7±4.29</td>
<td>85.45±3.94</td>
</tr>
<tr>
<td>(HbA1c)</td>
<td>6.44±0.436</td>
<td>6.36±0.48</td>
<td>6.53±0.38</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>24.67±2.38</td>
<td>26.72±3.22</td>
<td>26.74±2.96</td>
</tr>
<tr>
<td>Leptin</td>
<td>8.34±1.55</td>
<td>9.51±0.63</td>
<td>7.17±1.30</td>
</tr>
<tr>
<td>Uric acid</td>
<td>3.59±1.35</td>
<td>3.72±1.40</td>
<td>3.24±1.45</td>
</tr>
<tr>
<td>Glucose/leptin ratio</td>
<td>11.20±4.13</td>
<td>9.21±4.22</td>
<td>12.30±4.61</td>
</tr>
</tbody>
</table>

Results and Discussion

Table (1) shows the basic characteristics of subjects included in this study. One hundred forty diabetic patients had mean age equal to 45.63±6.11 years [mean ± SD] and one hundred non diabetic healthy subjects aged (49.41±5.72) years were served as controls. Biochemical tests results exhibit that the levels of fasting glucose, HbA1c, BMI and leptin were highly significant increased in patients when compared to healthy control subjects (p< 0.0001) and this result confirmed the previous observation studies [3,7,35].

Patients BMI were (26.89±4.87) Kg/m² so the patients were over weight. The prevalence of hyperuricemia has been increasing in recent years, not only in advanced countries but also in developing countries, along with the development of their economies. It has been suggested that hyperuricemia is associated with metabolic syndrome [32], in this study serum uric acid was highly increased in patient as ageneral than in control (p<0.0001), as well as the significant increased in uric acid in type II diabetes than in type I diabetes which observed in this study is support the researchers proposed that hyperuricemia has been found to be associated with obesity and insulin resistance and consequently with type II diabetes [1]. While Nan H,Dong et al in 2007 found that diabetic subjects have low serum uric acid than controls [33].

There are many ways to measure insulin resistance like Homeostasis Model Assessment...
for Insulin resistance (HOMA-IR) and Quantitative Insulin-Sensitivity Check Index (QUICKI), hyperinsulinemic euglycemic clamp tests and insulin suppression tests [36].

Recently, a number of studies have suggested that the fasting glucose to insulin ratio (G/I) may represent another useful method for assessing insulin resistance [35]. However, unlike HOMA or QUICKI, which are based on the product of fasting insulin and glucose, G/I does not appropriately reflect the physiology underlying the determinants of insulin sensitivity. The potential problems with using the fasting G/I ratio as a physiologically appropriate index of insulin sensitivity become apparent when fasting glucose levels are abnormal, The potential problems with using the fasting G/I ratio as a physiologically appropriate index of insulin sensitivity become apparent when fasting glucose levels are abnormal [37]. Because of highly correlation between insulin and leptin in patient with diabetes and because of the potential problems with using the fasting (glucose/insulin ) ratio as an index of insulin sensitivity,a new ratio between fasting(glucose/leptin ) was proposed to be used as an index for predicting diabetes mellitus when fasting glucose levels are abnormal by Raya Sulaiman et al [35], this study agreed with Raya Suliman as mentioned in Table (1), (glucose/leptin) found highly significant decrease in diabetes patients than in controls ( p< 0.0001).

Multiple regression analysis showed that the estimates of total body obesity and serum uric acid concentration are independently associated with serum leptin concentration for both healthy and diabetes. The finding of a highly significant positive correlation between serum leptin and uric acid levels suggests that leptin could be a pathogenic for hyperuricemia in obesity [27], this study observed that in patients group as a general without sex and type classification, a highly significant positive correlation was found between fasting uric acid and fasting leptin (p<0.001) as shown in Table (2) and Fig.(1).

### Table (2)

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>0.298*</td>
<td>0.012</td>
</tr>
<tr>
<td>FBS</td>
<td>0111</td>
<td>0361</td>
</tr>
<tr>
<td>Leptin(ng/ml)</td>
<td>0.482**</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI(kg/sqm)</td>
<td>0.176</td>
<td>0.145</td>
</tr>
<tr>
<td>Glucose/leptin</td>
<td>0.237</td>
<td>0.048</td>
</tr>
</tbody>
</table>

* Significant correlation when p<0.05; ** highly significant correlation when p <0.01 and r= correlation.

![Fig.(1) Positive correlation with linear regression equation between fasting serum uric acid and leptin. (R^2= 0.232, r=0.482, p<0.0001).](image)

The study of H. K. Choi and E. S. Ford found that Individuals with moderately elevated HbA1c levels (i.e. pre-diabetes) may be at a higher risk of hyperuricaemia and gout [38], the present study found a significant positive correlation between serum uric acid and serum HbA1c of patients (p<0.05) as shown in Table (2) and Fig.(2). In addition, a new correlation was proposed, this correlation is a significant negative correlation between serum uric acid and the ratio of (Glucose/leptin) of diabetes patients (p<0.05), Table (2) and Fig.(3).
Fig. (2) Positive correlation with linear regression equation between fasting serum uric acid and HbA1c. 
\( R^2 = 0.089, r=0.298, p<0.05 \).

Fig. (3) Negative correlation with linear regression equation between fasting serum uric acid and ratio Glucose/Leptin. 
\( R^2 = 0.056, r=-0.237, p<0.05 \).

In conclusion, Serum Fasting blood sugar, body mass index, HbA1c, leptin and uric acid were significantly increased in diabetes mellitus patient. Serum uric acid tend to increase with increasing serum leptin, and with increasing serum HbA1c of diabetes patients. But decrease with increase serum Glucose/leptin.

References


[31] H.K. choi and E.S. ford. Haemoglobin A1c,fasting glucose,serum c-peptide and insulin resistance in relation to serum uric acid levels –the third national health and nutrition examination survey.Rheumatology 2008; 74; 713-717, advance access publication.


الخلاصة

الهدف من هذه الدراسة كان لمقارنة مستوى مصل الدم من حامض اليوبريك و هيموكلورين في مرضى السكري، مع نسبة كلودوز / اللثين. تم إجراء الدراسة في المركز الوطني لمرض السكري في كلية الطب - الجامعة المستنصرية في الأول من شهر ابريل 2008 ولغاية الثلاثين من شهر كانون الثاني 2010. وكان عدد المرضى 140 بينما كان عدد الأسحاك 100 مع مراعاة تقارب الاعمار والجنس بين المجموعتين. تم قياس كمية السكر الصائم ، وحمض اليوبريك في مصل الدم بطرقية بطرقية المطياف في حين تم قياس هورمون اللثين بتقنية الفصل بالسائل العالي الإداة HPLC.

وتتم حساب كثافة الجسم (BMI) وحساب نسبة السكر الصائم/ اللثين. وقد وجد أنه مستوى حامض اليوبريك،