Effects of Type-2 Diabetes Mellitus on Serum Leptin, Insulin, Interlukin-8, and Lipid Profile

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Abstract

Background: Diabetes mellitus emerge as a developing global problem , insulin resistant occur to be prominent feature of type-2 diabetes mellitus, leptin hormone (which is a 167 amino acid protein synthesized in white adipocyte and directly proportionate with obesity) have a relationship with diabetes mellitus Type-2.while interlukin-8 (which is a chemotactic factor) may play a role in obesity or type-2 diabetes mellitus.

Objective: The aim of this study is to:

1-Determine the serum levels of Leptin, Insulin, Interleukin-8 (IL-8) and Lipid profiles in Type-2 diabetic Iraqi patients.

2-Evaluate the correlation between leptin, insulin, IL-8 and Lipid profiles in sera of Type-2 diabetes mellitus (T2DM) in Iraqi patients.

Materials and Methods: A total number of 95 (70 Type 2diabetic patients and 25 apparently normal subjects), (46male and 49 female) obtained from Al-Hussain Teaching Hospital/ Karbala - Iraq between Oct. , 2010 – April , 2011 with age ranged between (20-75) years how were divided into three groups: (obese type-2 diabetic patients, Non-obese type-2 diabetic patients, and Non-obese non-diabetic subjects) .Obese diabetic patients was specified by body mass index, BMI $\geq$30kg/m^2. Fasting serum leptin, insulin, IL-8 ,and lipid profile have been determined. A pre-tested questionnaire was designed to obtain information about age, gender, height, weight, and past-medical history. Body Mass Index (BMI) and (BF%) were the only anthropometric parameter specified.

Results and Discussion: The levels of each of leptin and insulin hormones, Cholesterol, LDL-cholesterol, TG, BMI and BF% were elevated markedly in diabetic patients compared with non-diabetic thin. Leptin hormone level shows a significant positive correlation with insulin hormone, LDL-cholesterol, BMI and BF%. The level of IL-8 was fluctuated and there is a non-significant positive correlation with increasing BMI. Significant differences were found in leptin mean values between male and female in which its levels is markedly elevated in females.

Conclusion: The results obtained in this study reveals significant elevations in serum leptin, insulin, cholesterol, and LDL-cholesterol with a non-significant decline in HDL-cholesterol in Type2 diabetic patients in comparison with normal subjects. Also there was a significant elevation in serum leptin level in females in comparison with males in both diabetic and control groups. There was a non-significant positive correlation between IL-8 and obesity. The results show a strong correlation between insulin resistant and leptin resistant.

الخلاصة

الخلفية: يعتبر داء البول السكري من الأمراض الشائعة في الوقت الحاضر. ولغرض الوقوف على أحدث المتغيرات البايوكيميائية في أمصال مرضى البول السكري من النوع الثاني ومن البد نا ء فقد أجريت هذه الدراسة.

الهدف : إن الهدف الرئيسي هو متابعة المتغيرات في مستويات كل من (هرمون النحافة , الانسولين والانترلوكين -8 إضافة إلى متابعة المتغيرات البايوكيميائية التي تحصل في مستويات الدهون وإيجاد العلاقة فيما بينهم.

المواد وطرق العمل: أجريت هذه الدراسة على خمس وتسعين شخص (سبعين مريض بداء السكر من النوع الثاني وخمس وعشرين شخص سوي أاعتبرو ا كمجموعة سيطرة). ألمجموعه بكاملها كان فيها ست وأربعين ذكرا وتسع وأربعين أنثى .

تم الحصول على عينات الدم من مجموعة المرضى ومجموعة السيطرة في مستشفى الحسين (ع) التعليمي في مدينة كربلاء . تم الحصول على أمصال الدم وتم متابعة تأثير داء السكر من النوع الثاني على هرموني النحافة و الأنسولين والانترلوكين- 8 والكوليستيرول الكلي و البروتينات الدهنية عالية الكثافة و الكليسيريدات الثلاثية والبروتينات الدهنية واطئة الكثافة جدا و البروتينات الدهنية واطئة الكثافة

النتائج ومناقشتها: أظهرت نتائج هذه الدراسة حدوث زيادة ملحوظة في تركيز هرمون النحافة وهورمون الانسولين والكولسترول الكلي و الكليسيريدات الثلاثية و البروتينات الدهنية واطئة الكثافة و نقصان في البروتينات الدهنية عالية الكثافة عند مرضى السكري من النوع الثاني مقارنة بمجموعة السيطرة. كذلك أظهرت هذه الدراسة زيادة ملحوظة في تركيز هرمون النحافة في أمصال النساء المصابات بداء السكر واللواتي تعاني أجسامهن من البدانه مقارنة بالرجال المصابين بالسكر والبدانه وحدوث زيادة ملحوظة في هرمون النحافة تتزامن مع الزيادة في مؤشر كتلة الجسد.

Introduction

Diabetes Mellitus is epidemic in Asia Characterized by rapid rates of increase over short period and onset at a relatively young age and low BMI. The epidemic is heterogeneous, varying according to different ethnic and cultural subgroups, degree of urbanization, and socioeconomic conditions in different Asian populations. In parallel with economic development and nutrition transition, the rates of overweight and obesity have been increasing rapidly in Asian countries. Abdominal or central adiposity, particularly detrimental to type 2 diabetes and other metabolic diseases, is highly prevalent in Asians. The high rates of gestational diabetes, childhood obesity, and over nutrition in later life, may contribute substantially to the increasing diabetes epidemic in Asia [1].

Type 2 diabetes mellitus or non-insulin dependent diabetes mellitus (NIDDM) is characterized by insulin resistance which may be combined with relatively reduced insulin secretion.The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor [2]. However, the specific defects are not known. In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity [3]. Type 2 diabetes is the most common type of diabetes, accounting for 90-95% of all diabetes [4]. It usually develops after the age of 40. However, in the late 1990's, its incidence increased among young people.Experts is trying to determine why that is happening; they think it may be related to the increased incidence of obesity and sedentary lifestyles among young people in the USA. About 80% of those with type 2 diabetes are overweight [5, 6]. It is more common among people who are older, sedentary or obese, or have a family history of the disease [7].

Obesity and increasing body weight lead to accumulation of fat in the liver, a condition known as nonalcoholic fatty liver disease (NAFLD). The result of NAFLD is an excessive

release of free fatty acids into the bloodstream (due to increased lipolysis), and an increase in hepatic glucose production, both of which have the effect of exacerbating peripheral insulin resistance and increasing the likelihood of Type 2 diabetes mellitus also secretion of adipokines (a cytokines secreted by adipose tissue) that impair glucose tolerance. Abdominal fat is especially active hormonally. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes [8,9].

Human leptin is a protein of 167 amino acids. It is manufactured primarily in the adipocytes of white adipose tissue, and the level of circulating leptin is directly proportional to the total amount of fat in the body [10, 11]. Leptin plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism [12, 13]. It is one of the most important adipose derived hormones. The aim and novelty of the present study was to investigate the possible relationships between plasma leptin levels and T2DM with or without obesity [14].

Materials and Methods

This study was conducted at Al-Hussain Teaching Hospital/ Kerbala; Samples were randomly selected from the patients attending the Diabetic Consultation Unit at the Hospital during the period from Oct., 2010 – April, 2011 with age ranged between (20-70) years (Male and Female). A total number of 95 cases (70diabetic patients, 34 male and 36 female; and 25apparently healthy subjects as control group, 12 male and 13 female) classified according to obesity and/or type 2 diabetes mellitus into three categories:

1- Type-2 diabetic patients whose body mass index (BMI) $\geq$ 30 kg/m^2.
2- Type-2 diabetic patients whose BMI $\leq$25 kg/m^2.
3- Non-diabetic subjects whose BMI $\leq$25 kg/m^2.

Measurement of serum leptin, insulin, and interlukin-8 and lipid profile has been done by specified kits.

To compare the significant of the difference in the mean values of the two groups, student's t-test was applied; $p < 0.05$ was considered statistically significant. We compare the diabetic patient with non-diabetic control group. The correlation coefficient r-test is used to describe the association between the different studied parameters; $p < 0.05$ was considered statistically significant.

Results and Discussion

Effect of Type 2 Diabetes Mellitus on Serum Leptin.

Our results shows that serum leptin was significantly high in Type 2 diabetic patients group compared with non-diabetic non-obese control group examined with a 2-tail student's t-test statistical analysis ($P<0.001$) as shown in Table-1.

Serum leptin correlates positively and strongly with serum insulin ($r = 0.294$) and LDL- cholesterol ($r = 0.293$). Its level correlate positively and strongly with serum cholesterol, BMI and BF% at 0.01 level of significant ($r=0.320$, $r=0.641$, $r=0.634$) respectively and also with gender (female sex) at same level of significant. While it correlate positively but non-significantly with IL-8. Serum leptin correlate non-significant negatively with serum HDL- cholesterol ($r= -0.204$).

Our results are in good agreement with previous literatures regarding the role of leptin in diabetes [15], nevertheless

other reports indicate decreased [16- 19] or unchanged [20, 21] leptin levels in T2DM.

Table 1. Mean ± SD values of Leptin, Insulin, IL-8, Triglycerides, Cholesterol, HDL-C, LDL-C, Body mass index and Body fat% in Type-2 diabetic patients as compared to non-diabetic non-obese control group.

Marker	Diabetic patients (N=70)	Non-Diabetic non-Obese (N=25)	P value
Leptin (ng/ml)	23.1±2	1.9±0.6	< 0.001
Insulin (µ IU/ml)	20.0±4.3	11.4±3.1	< 0.05
IL-8 (pg/ml)	32±4.6	28.5±2.6	NS
Cholesterol (mg/dl)	214.5±47	153.7±27.7	< 0.05
TG (mg/dl)	148.5±21.9	82.7±22.1	< 0.05
LDL (mg/dl)	140.1±25.1	100±24.8	< 0.05
HDL (mg/dl)	42.5±10.7	44.9±6.4	NS
BMI (kg/m^2)	32.9±10.2	20.6±3.9	< 0.001
BF%	40.4±17.6	19.9±6.3	< 0.001

Part of the controversy among previous reports could be related to the differences in adiposity or gender of the patients [22]. The elevated leptin level in T2DM could be contributed to:

1- Leptin concentration is modulated by weight gain and loss in adult humans. Obesity is strongly associated with development of T2DM. Adipose-derived hormone, leptin has been implicated in the regulation of body weight and energy homeostasis. Circulating leptin concentrations reflect the amount of adipose tissue in the body [24, 25], and as we know the strong relationship between T2DM and obesity so the elevated leptin might be due to increased body mass.

2- Leptin is a hormone made by adipocytes and mainly acts centrally to control body weight [26]. It conveys information to the brain about the size of energy stores and stimulates the hypothalamic centers responsible for regulation of energy intake and expenditure [27]. A hypothesis of leptin resistance at the level of the hypothalamus resulting in an increase appetite and decrease energy expenditure despite adequate leptin production in the adipocyte [23]. (No feedback inhibition).

3- The elevated insulin level in T2DM stimulates leptin expression/ release (Saladin et al., 1995; Wabitsch et al., 1996) [28, 29].

Regarding lipid profiles, our results are in a good accordance with Asakawa et al.1999 [30] in which leptin has independent effects on lipid metabolism .Furthermore, he reported inverse correlation between leptin and HDL-cholesterol.

The gender difference in leptin level might be due to:

1- Women tend to have a higher overall obesity which is more pronounced in subcutaneous fat than in visceral fat, in contrast to men who have a lower overall but greater visceral adiposity [31].women have more body fat than men and different fat distribution

2- Leptin mRNA expression is higher in subcutaneous adipocytes than in omental, retroperitoneal, and mesenteric adipocytes and this difference is larger in women than in men. This may partially explain the gender differences in leptin levels between male and female [32].

3- Corticosteroids (Wabitsch et al., 1996) [29] and estrogens (Shimizu et al., 1997) [33] also exert a stimulatory effect on leptin secretion, at least on

female adipocytes (Casabiell et al., 1998; Pineiro et al., 1999) [34]. Both androgens (Jockenhovel et al., 1997, Pineiro et al., 1999) [35] and β3-adrenergic agonists (Collins and Surwit, 1996) [36] inhibit leptin production.

Effect of Type 2 Diabetes Mellitus on Serum Insulin.

Our results shows that serum insulin mean value was significantly high in type 2 diabetic patients compared with non-diabetic non-obese control group , the statistical analysis has been done with a 2-tail student's t-test ($P<0.05$) as shown in Table-1.

Serum insulin have strong positive correlation with BF% at 0.05 level of significant ($r = 0.258$). It also have a positive non-significant correlation with IL-8, Cholesterol, LDL-cholesterol and BMI ($r=0.164$), while it correlate negatively with HDL cholesterol ($r = - 0.031$).

Our results are in consistent with previous reports [37] in which Insulin resistance increases with increasing body mass index, and waist circumference. These reflect increased adiposity especially increased levels of visceral adipose tissue.T2DM is characterized by defects in insulin secretion and insulin action. , Leptin also influences insulin sensitivity and insulin secretion [38]. In diabetes, plasma leptin levels are confounded by factors that affect insulin sensitivity and insulin secretion such as hypoglycemic drugs and diet [16].T2DM and the Metabolic Syndrome would be the most common clinical syndromes associated with insulin resistance. Insulin resistance typically predates the development of diabetes and is commonly found in unaffected first-degree relatives of diabetic patients [39].

Effect of Type 2 Diabetes Mellitus on Serum IL-8.

Although serum IL-8 mean value was high in Type 2 Diabetic patients than non-diabetic non-obese control group ,but it shows no significant difference between them examined with a 2-tail student's t-test statistical analysis ($P>0.05$) as shown in Table1.

IL-8 shows non-significant positive correlation with cholesterol, LDL-cholesterol, HDL-cholesterol, BMI and BF% ($r=0.089$).While it shows a negative correlation with TG-cholesterol.IL-8 besides its implications for its association with different inflammatory processes and because the adipose tissue is able to produce and release various cytokines and IL-8 has been implicated in the atherosclerotic process [40,41], we found it is of interest to investigate the ability of human adipose tissue and isolated adipocytesto express and release IL-8 and we will discuss that by discussing the combined effect of diabetes and obesity.

Effect of Type 2 Diabetes Mellitus on Serum Lipid Profile.

Serum cholesterol, LDL-C and TG were significantly high in T2 Diabetic patients group than non-diabetic non-obese control group examined with a student's t-test statistical analysis ($P<0.05$) ,while serum HDL-C level was low in T2DM than non-diabetic non-obese control group but it shows no significant difference examined with a student's t-test statistical analysis as shown in Table-1.

Firstly, serum cholesterol shows a strong positive correlation with LDL-cholesterol at 0.01 level of significant ($r=0.919$), and with BMI and BF% at 0.05 level of significant ($r=0.424$) ($r=0.417$) respectively.

Secondly, TG-cholesterol shows a non-significant negative correlation with

HDL-cholesterol (r= -0.207) as shown in figure and a non-significant positive correlation with LDL-cholesterol, BMI and BF%.

Thirdly, LDL-cholesterol has a non-significant positive correlation with BMI and BF% and a non-significant negative correlation with HDL-cholesterol.

Finally, HDL cholesterol shows a non-significant negative correlation with each of BMI(r= -0.063) and BF% (r= -0.094).

BMI correlate positively and strongly with BF% at 0.01 level of significant (r=0.928), BF% correlate positively and strongly with gender (female sex) at 0.05 level of significant.

Our results are in a good agreement with the majority of previous reports [42].The lipid abnormalities associated with insulin resistance affect all lipid fractions. They are characterized by elevated fasting triglyceride levels, elevated postprandial triglyceride rich remnant lipoproteins, low HDL cholesterol, and small dense LDL particles. This pattern correlates strongly with cardiovascular risk, and treatment decreases this risk. The negative correlation between serum leptin level and HDL cholesterol in our results [r = -0.204, P < 0.05], is consistent with other authors [43, 44].

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