ORIGINAL ARTICLE

Relationship Between Insulin like Growth Factor-1 and Leptin in Type II Diabetic Patients

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Diabetes is a common endocrine disease in humans. Leptin secretion is influenced by many factors and although the growth hormone/insulin like growth factor (GH/IGF) axis plays an important role in the regulation of body composition, the physiological interaction between Leptin and IGF-1 system remain unknown. The aim of this study was to investigate the correlation between Leptin and IGF-1 in type II diabetics and controls.

Materials and Methods: This case-control study was consisted of 38, type 2 diabetics (20 males and 18 females, mean age 49.33 ± 11.33,years) and 46 healthy controls (16 males and 30 females, mean age 49.52 ± 7.99,years). We measured the concentrations of fasting plasma glucose (FPG), IGF-1, hemoglobin A1C (HbA1c) and insulin like growth factor binding protein-3(IGFBP-3) in both groups. FPG was measured by the enzymatic glucose oxidase method and the Hb Gold analyzer HPLC was used to measure $HbA1_C$. For determination of leptin, IGF-1, IGFBP-3 and insulin concentrations, the enzyme linked immunosorbent assay (ELISA) method was used. P< 0.05 was considered statistically significant.

Results: Means of BMI and age did not differ significantly between the two groups. Mean serum levels of IGF-1, leptin, insulin, FPG and HbA1c concentrations in type 2 diabetics were significantly higher than in controls (p<0.05). In both groups, mean serum levels of leptin in males, were statistically lower than in females. Strong correlations were found between IGF-1 and IGFBP-3, leptin and insulin, IGF-1 and age, and between BMI and FPG in both patients and controls (p<0.05). A negative correlation was observed between IGF-1 and HbA1c in patients and controls (p< 0.05).

Conclusion: It is concluded that leptin and the IGF-1 system, could influence body composition and fat content, particularly in obese and overweight diabetic patients.

Key Words: Type II diabetes, Leptin, IGF-1, IGFBP-3, IGF-1/IGFBP molar ratio

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Introduction

The incidence of diabetes, a serious health problem worldwide is increasing dramatically. In addition, overweight and obesity results in health disorders in diabetic patients.[1] The pathogenesis of obesity remains largely unknown, but research on its pathophysiology has recently intensified, following the discovery of leptin. However, accumulating evidence suggests that the role of leptin is much broader than that of an antiobesity hormone. Leptin also affects several neuroendocrine mechanisms.[2, 3]

Leptin, a 16-KD protein secreted from white adipocytes, has been implicated in the relation of food intake[5] energy expenditure and whole-body energy balance in rodents and humans. The expression and secretion of leptin is highly correlated with body fat mass and adipocte size.[6] Insulin and cortisol are potent stimulators of leptin expression and the role of other hormones and growth factors in the regulation of leptin expression and secretion is coming to light. [7, 8] The plasma level of leptin has a positive correlation with body mass index in rodents and humans. It has also been reported that insulin may interact with the control of leptin gene expression in diabetic rats and controls.[9] Leptin injections in diabetic rats may improve the sensitivity of insulin receptors and in decreasing blood glucose level.[6, 10]

Insulin like growth factor (IGF-1), a protein with 7.6–kD and 70 amino acids, has a 48 % similarity with proinsulin.[11] More than 99% of plasma IGF-1 circulates bound to IGF-binding protein-3 (IGFBP-3) and forms a large 150-kDa complex that cannot leave the circulation;[12] thus, only the unbound form of IGF-1 is considered to be biologically active.[13] Recently, the IGF-1/IGFBP-3 molar ratio has been indicated to reflect the amount of unbound and biologically active IGF-1.[13] Growth hormone indirectly controls IGF-1 production in liver tissue and mediate the actions of GH.[14] It has been shown that leptin causes high secretion of GH, whereas IGF-1 decrease leptin mRNA expression.[15] Although these findings demonstrate that leptin could be located in regulatory loop of GH/IGF-1 axis, other studies show that IGF-1 mRNA expression, along with leptin mRNA were increased in response to GH injections in sheep tissues.[7,16]

The GH/IGF axis-leptin association is thought to play an important role in the regulation of body functions throughout life.[17] Although, the association between these two is influenced by different factors, the physiological interaction is yet to be determined.[4] In the pathogenesis of diabetes and obesity, many hormonal and genetic disorders including variations in leptin secretion, expression, receptor defect and functionality are involved. On the other hand, IGF-1 may play an important in this process because of involvement in the insulin /GH axis.[10-12]

Although the association of these two hormonal systems by anthropometric and body composition variables has been repeatedly investigated, the physiological interactions between leptin and the GH/IGF-1 system remain unclear. We hypothesized that plasma leptin concentrations may be correlated to IGF-1 in type 2 diabetes. Therefore, this study was performed to examine the relationship between plasma leptin and IGF-1 along with anthropometric variables in type II diabetes mellitus

Materials and Methods

The study group consisted of 38 patients, diagnosed with type 2 diabetes (20 male and 18 female, mean age 49.33±11.13 years), and referred to the endocrine department of the diabetic clinic in the Sina teaching hospital, Tabriz University of Medical Sciences. Exclusion criteria were subjects with known diseases associated with disordered glucose metabolism (e.g. Cushing's disease), pancreatectomy, subjects with past or present thyroid dysfunction or those treated with thyroid hormones or currently pregnant, subjects on glucose altering medications, including glucocorticoids, thiazides, interferon-α, retroviral agents and anti-neoplastic agents; also excluded were subjects with chronic disease such as kidney, heart and hepatic diseases. In the present analysis, the American Diabetes Association criteria (ADA, fasting se-

rum glucose level ≥126 mg/d L or treated with antidiabetic agents) were used to diagnose diabetes mellitus, from venous glucose levels. The control group included 46 non-diabetic healthy individuals (16 male and 30 female, mean age 46.52±7.99 years), who had annual health check-ups in the Sina teaching hospital, Tabriz University of Medical Sciences. The following criteria were used to select the control group: No diabetes in their first degree relatives, fasting plasma glucose concentration less than 110 mg/dL, and hemoglobin A_{1C} concentration below 6%. Subjects with endocrine disease, significant renal or hepatic disease, and those receiving medication for disordered glucose metabolism, hypertension or hyperlipidemia, were excluded from the study. Written informed consent was obtained from each subject and the institutional review board of Tabriz University approved the study protocol according to the Declaration of Helsinki.

Anthropometric measurements and sampling

All individuals were asked to complete a self questionnaire on anthropometric characteristics, general health, smoking, alcohol consumption, and present medications, including hormone replacement, oral hypoglycemic agents and oral contraceptive treatment. Weight was measured by a Sega scale (made in Germany) with 0.5 kg accuracy. Waist circumference was defined as the smallest girth midway between the lowest rib margin and the iliac crest. BMI was calculated as weight (kilograms) divided by height squared (square meters). Obesity was defined as BMI≥30 kg/m^2, and overweight was defined as $24.9 \leq BMI \leq 29.9$ kg/m^2. Blood samples were collected (10 mL) after 8-12 hours fasting in a sitting position from the antecubital vein. Sera that were separated immediately after centrifugation with 3000 x g for 10 min were stored at -70 °C until the assay for clinical measurements was performed.

Laboratory Measurements

Fasting blood glucose (FPG) was measured by the glucose oxidase method (Pars Azmun. Tehran, Iran). Intra and inter-assay coefficients of variation for measuring glucose were 0.84% and 1.28%. HbA1c was measured in both patients and controls by Hb gold analyzer with high performance liquid chromatography on reversed phase partition ion exchange chromatography, with the coefficient of variation (CV) below 5%. Serum leptin level was measured by the sandwich and competition kind of ELISA, using recombinant human leptin and two special antibodies (IBL. Tokyo, Japan). Intra- and inter-assay coefficients of variation for measuring leptin were 5.1% and 7.8%, respectively. Serum concentrations of insulin like growth factor, after extraction using the ethanol acid method by ELISA (Bio source. Belgium), were measured. Intra- and inter–assay coefficients of variation were 8.03 and 12.76%, respectively. Serum level of IGFBP-3 was measured using ELISA and two special antibodies with high affinity for two different epitopes (Bio source. Belgium). Intra- and inter–assay coefficients of variation were 6.5 and 9.13%, respectively. Serum levels of insulin were measured by ELISA, using a commercially available kit (Monobind, USA,) including high affinity antibody and special enzyme conjugate. Intra- and inter–assay coefficients of variation were 8 and 8%, respectively. Stat Fax® 2100 ELISA reader was used for all hormonal measurements.

Statistical analysis

All continuous data are expressed as mean±S.D. Statistical analysis was done using SPSS for windows, version 14 software. Leptin and other variables levels of non-diabetic and diabetic group were compared using the Student's independent samples t-test. Correlations of leptin levels with the other parameters were evaluated by the Pearson correlation coefficient. For all statistical assessments, $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics including age, length of disease, FPG, HbA1c, Insulin, IGF-1, IGFBP-3, Leptin, and BMI in the two groups are presented in Table 1.

Differences in age and BMI between the two groups were not statistically significant. The length of disease in diabetic patients ranged between 1 to 95 months (mean 70.6 months). Regarding medication for glucose control, 10 patients used metformin, 4 patients Sulfonylurea, and 10 both drugs; 14 used no medication. Six of the diabetic patients and 4 controls were smokers. The mean concentrations of leptin and IGF-1 in diabetic patients were significantly higher than in non-diabetics ($p<0.05$). The mean concentration of FPG, insulin and percent of HbA1c were also higher in diabetic patients than in nondiabetics, difference statistically significant ($p<0.05$). However, mean serum levels of IGFBP-3 showed no significant differences between the two groups ($p>0.05$). Mean concentration of leptin in women was significantly higher than in men in the diabetic (25.4±15.7 vs.13.6 ±8.6) and non-diabetic (12.97±8.6 vs. 6.± 4.8) groups (Table 3). Whereas, the differences in other variables were not statistically significant between diabetic and non-diabetic groups ($p>0.05$) (Table 1), we did observe a significant difference between mean serum levels of leptin in overweight and obese subgroups in both groups ($p<0.05$) (Table 2).

Table 1. Clinical characteristics and serum levels of leptin, IGF-1, IGFBP-3, insulin, FPG, HbA1c, BMI in type 2 diabetic patients and non-diabetic groups

Variables	Non-diabetic (n=46)	Diabetic (n=38)	P value
Age (yr)	49.52±7.99*	49.33±11.33	0.892
BMI (kg/m2)	29.80±3.91	31.3±3.35	0.425
Waist (cm)	98±13	104±7	0.266
Leptin (ng/mL)	11.23±8.30	19.25±12.70	0.001
Total IGF-1 (ng/mL)	188±82	245±103	0.007
HbA1c (%)	4.63±1.31	7.61±2.09	0.001
Insulin (μIU/mL)	4.76±2.88	14.24±9.56	0.001
FPG(mg/dL)	98±13	149±74	0.001
IGF-1/IGFBP-3 molar ratio	0.35±0.16	0.54±0.15	0.004
IGFBP-3 (ng/mL)	2472±1088	2795±1180	0.340

* Mean±SD; BMI, body mass index; IGF-1, Insulin like growth factor-I; HbA1c, Glycated hemoglobin; FPG, fasting plasma glucose; IGFBP-3, Insulin like growth factor binding protein-3

Table 2. Comparison of mean serum level of leptin, IGF-1, IGFBP-3, insulin, FPG, HbA1c, BMI in overweight and obese subjects of diabetic and non-diabetic Groups

Variables	Non-Diabetic			Diabetic		
	Ov	Ob	P	Ov	Ob	P
Age (yr)	49.2±11.1*	46.7±10.2	0.369	45.69±5.6	49.12±11.2	0.201
BMI (kg/m2)	27.4±1.2	31.4±3.4	0.130	29.05±3.1	31.8±3.2	0.641
Waist (cm)	99.1±13.4	110.1±12.2	0.098	92.42±7.26	114.1±11.0	0.54
Total IGF-1 (ng/mL)	137.7±65.2	197.5±74.4	0.07	241.62±90.5	266.0±85.8	0.06
IGFBP-3 (ng/mL)	1822.1±598.21	2647.5±1203.3	0.01	2783.7±1121.2	3832±1397.4	0.03
Leptin (ng/mL)	6.0±4.4	14.15±8.3	0.006	19.19±5.4	29.23±12.8	0.003
FPG (mg/dL)	98.2±13.8	101.6±10.9	0.099	149.5±35.4	164.12±86.2	0.102
Insulin (µIU/mL)	7.12±2.9	8±2.93	0.641	10.4±9.5	11.8±8.2	0.620
IGF-1/IGFBP-3 Molar ratio	0.39±0.20	0.41±0.10	0.369	0.49±0.5	0.54±0.15	0.280

Ov, Overweight; Ob, Obese; * Mean±SD

Table 3. Clinical characteristics and anthropometric indices in males and females of diabetic and non-diabetic groups

Variables	Diabetic		Non-Diabetic	
	Male (n=20)	Female (n=18)	Male (n=16)	Female (n=30)
Age (years)	51.3±11.4†	52.7±13.3	45.4±10.0†	36.8±9.6
BMI (kg/m2)	29.9±4.1†	31.9±2.9	29.5±3.4†	30.7±3.2†
Waist (cm)	103±8†	104±7	95±12†	99±13
IGF-1 (ng/mL)	217±85†	267±115†	190.5±74†	188±86
IGFBP-3 (ng/mL)	2626.6±1097†	2982.3±1270	2543±704†	2447±1203
FPG (mg/dL)	157±91†	134±50†	106±10	97±13
HbA1c (%)	7.5±2.1†	7.6±2.1	4.6±1.5†	4.6±1.2
Leptin (ng/mL)	13.6±8.6**	25.4±15.7	6.3±4.8**	12.9±8.6
Fasting Insulin (µIU/mL)	13.3±9.7†	15.1±9.5	5.0±2.9†	4.6±2.9

**The mean differences between male and female in each group were significant (P< 0.05). †The mean differences between male and female in each group were not significant (P>0.05).

However, the IGF-1/IGFBP-3 molar ratio was not significantly different between these two subgroups ($p<0.05$). There was a significant and direct correlation between IGF-1 and IGFBP-3 in the diabetic ($r = 0.766$, $p \leq 0.001$) and non-diabetic ($r=0.797$, $p \leq 0.001$) groups (Fig. 1). A negative correlation was observed between IGF-1/IGFBP-3 molar ratio and leptin in diabetic and non-diabetic groups ($p<0.05$) (Fig. 2). There was a positive and significant correlation between serum levels of leptin and insulin in the diabetic group ($r=0.49$, $p<0.05$), while there was a significant negative correlation with the non-diabetic group ($r = -0.305$, $p<0.05$) (Fig. 3). Although there was a significant and direct correlation between IGF-1 and HBA1c in the non-diabetic group ($r=0.39$, $p<0.05$), the correlation was not significant in the diabetic group ($p>0.05$). There was a significant and direct correlation between BMI and leptin in non-diabetic subjects ($r=0.422$, $p<0.05$) (Fig. 4). A reverse trend correlation was observed between IGF-1 and age in both groups.

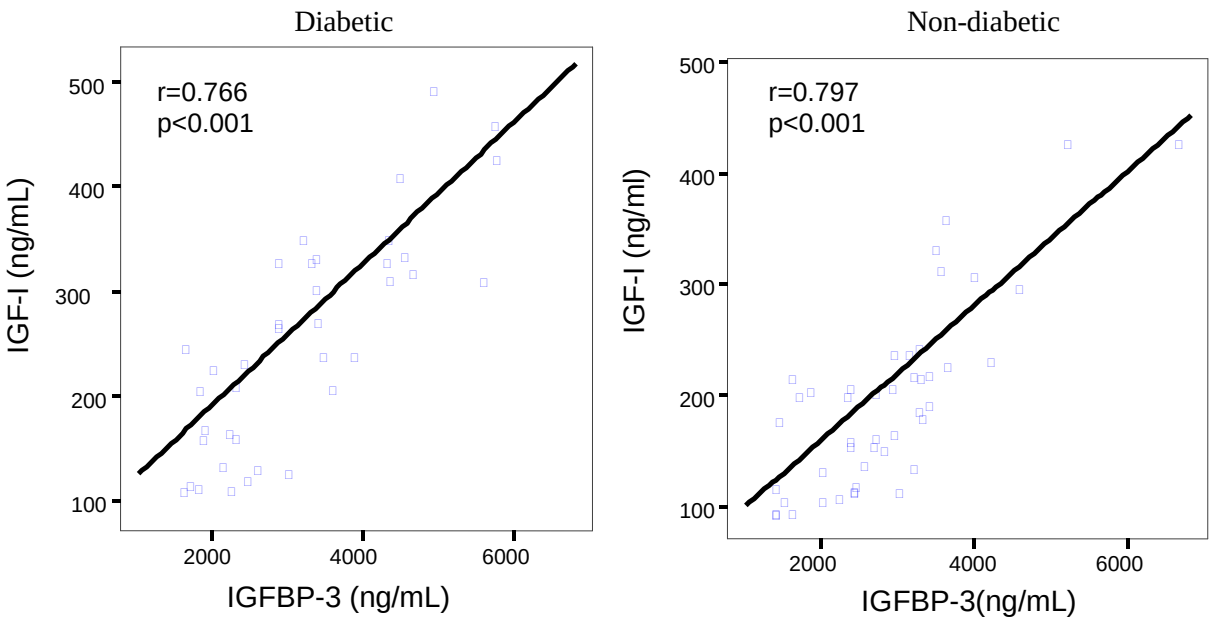

Fig. 1. Correlation between serum levels of IGF-1 and IGFBP-3 in diabetic and non-diabetic groups

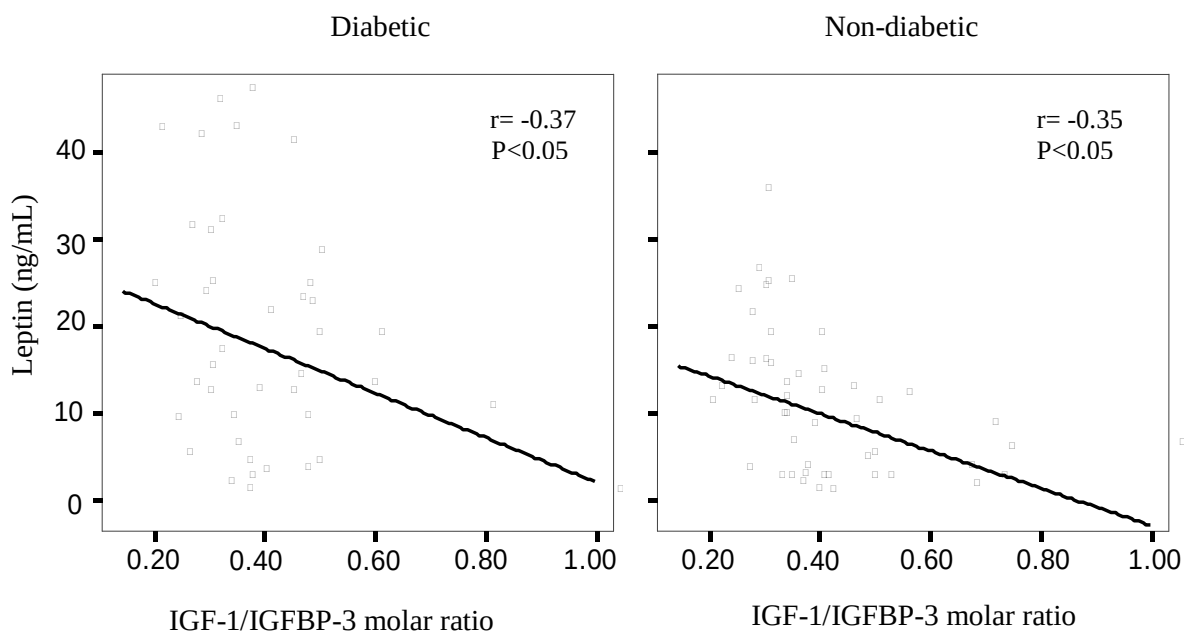

Fig. 2. Correlation between serum leptin levels and IGF-1/IGFBP-3 molar ratio in diabetic and non-diabetic groups

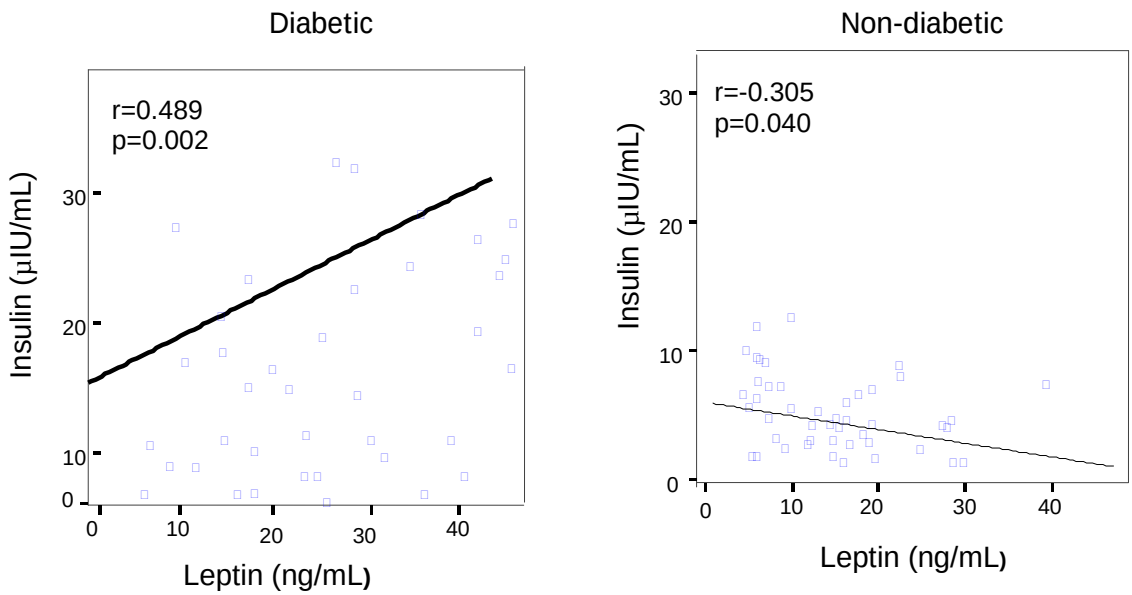

Fig. 3. Correlation between serum levels of leptin and insulin in diabetic and non-diabetic groups

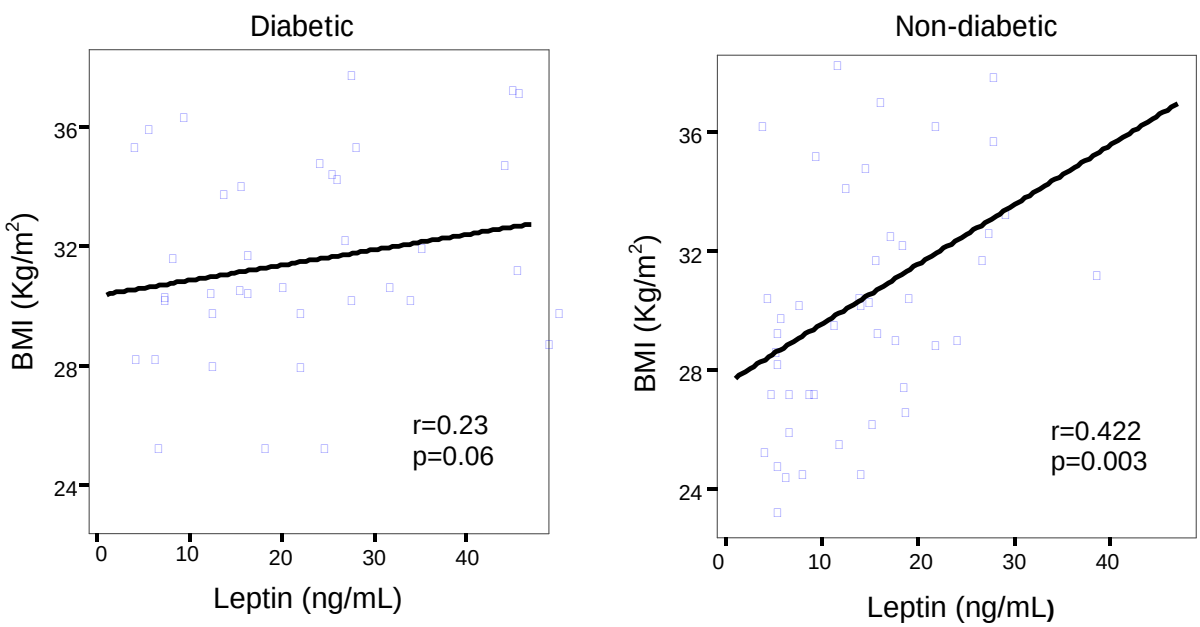

Fig. 4. Correlation between serum levels of leptin and BMI in diabetic and non-diabetic groups

Discussion

Leptin secretion is influenced by many hormonal and metabolic factors[18, 19] but their respective roles in the overall regulation of leptin production have not been fully ascertained. Besides a close correlation to BMI, leptin secretion has been suggested to be modulated by insulin, [19] thyroid hormones[20] and supply of dietary energy.[19, 20] The results of the present study confirm that body composition and insulin variables affect leptin regulation. In agreement with results documented by some authors, we found an age related, but not gender related difference in IGF-1 concentrations, both in overweight and obese subjects. Moreover, some reports show that there is a relationship between serum concentrations of leptin and IGF components in lean elderly subjects.[21] we found a negative correlation between IGF-1/IGFBP3 molar ratio with age, leptin and BMI in overweight and obese subjects. IGF-1 concentrations are markedly reduced in malnutrition and anorexia nervosa, [22] as well as in catabolic states. However our present findings in type 2 diabetic patients confirm that IGF-1/IGFBP3 molar ratio is inversely related to BMI and higher than those in controls. Typically obese, nondiabetic individuals have elevated levels of leptin.[16] Interestingly, several studies have reported that type 1 diabetic patients have significantly lower leptin levels compared to nondiabetic subjects, after controlling for age and body fat percentage.[23] In fact, leptin has been found to inhibit insulin receptor autophosphorylation.[24] In our study, patients with type 2 diabetes mellitus were found to have higher levels of leptin than healthy individuals. In addition, a negative correlation was found between the percentage of HbA1c and IGF-1/IGFBP3 molar ratio. A significant decrease in the circulation levels of IGF-1, which returns after insulin treatment to normal range, was observed in poorly controlled IDDM type 1 subjects.[25] In addition, in insulin resistance patients, serum levels of IGF-1 are low[26] but in a recent study, the total IGF-1 and IGF-1/IGFBP3 molar ratio was higher in type 2 diabetic patients. In conclusion, attention however must be paid to evidence showing that total IGF-1 concentrations do not necessarily reflect IGF-1 activity.[27] An increase in IGF-1/IGFBP3 molar ratio has been recently reported in obese patients.[28]This finding could be explained by the reduction in IGFBP-3 concentrations which, in turn, could be caused by hypoinsulinemia.[26,28] We found that the regulation of leptin in response to stress appears to be complicated and may depend on many factors including the duration and metabolic status. Furthermore, leptin may also be directly involved in the pathophysiology of type 2 diabetes mellitus. In summary, it is speculated that serum leptin and IGF-1 levels in patients with type 2 diabetes were increased compared to the non-diabetic control group. Thus, leptin most likely plays a role in the pathophysiology of type 2 diabetes mellitus, particularly in obese individuals.

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