Association of leptin with insulin resistance, body composition, and lipid parameters in postmenopausal women and men in type 2 diabetes mellitus

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ABSTRACT

الأهداف: لتحديد ارتباط عنصر اللبتين بمقاومة الأنسولين، وتركيب الجسم، ونسبة الدهون لدى النساء والرجال المصابين بداء السكري من النوع الثاني (T2DM).

الطريقة: أجريت هذه الدراسة على 158 مريضاً (87 امرأة في مرحلة انقطاع الطمث، و71 رجل) مصابين بداء السكري من النوع الثاني (T2DM)، مع 99 شخصاً سليما يمثلون مجموعة التحكم (52 امرأة في مرحلة انقطاع الطمث، و47 رجل). تم اختيار المرضى المصابين بداء السكري من النوع الثاني (T2DM) تعاقبياً من العيادات الخارجية للغدد الصماء بجامعة كومهوريات – تركيا، في الفترة ما بين أبريل 2002م وحتى مارس 2005م. قمنا بجمع القياسات السكانية، ومستوى اللبتين، ومقاومة الأنسولين، وتركيب الدهون والجسم.

النتائج: كانت مستويات مصل اللبتين لدى النساء أعلى بشكل ملحوظ من الرجال المشاركين في كلتا المجموعتين المصابين بداء السكري من النوع الثاني (T2DM)، والأصحاء في مجموعة التحكم. كان معدل الاستقلاب القاعدي، وكتلة الدهون، وإجمالي الماء في الجسم للذكور أقل من الإناث في كلتى المجموعتين المصابين بداء السكري من النوع الثاني (T2DM)، والأصحاء في مجموعة التحكم، كما كان اللبتين على صلة إيجابية مع مقاومة الأنسولين وقياسات تركيب الجسم في كلى الجنسين. كانت مستويات مصل اللبتين لدى النساء أعلى بالمقارنة مع الرجال في نفس قياس كتلة الجسم المستقل (BMI) من داء السكري من النوع الثاني (T2DM).

خاتمة: لدى اللبتين ارتباط بالأنسولين (HOMA–IR, HOMA–ß) وقياسات تركيب الجسم (BMI, BMR, BW, %fat, and FM) لدى المشاركين في الدراسة مع/أو بدون الإصابة بداء السكري من النوع الثاني (T2DM) في كلا الجنسين. يبدو أن داء السكري من النوع الثاني (T2DM) أكثر فعالية على مقاومة الأنسولين من البدانة. نقترح أن جنس الإناث وكتلة الدهون قد يكون له تأثير ذو معنى على مستويات اللبتين في السن ولكن ليس داء السكري من النوع الثاني (T2DM).

Objective: To determine the association of leptin with insulin resistance, body composition, and lipid parameters in postmenopausal women and men with type 2 diabetes mellitus (T2DM).

Methods: This study was conducted in 158 patients (87 postmenopausal women and 71 men) with T2DM, and 99 healthy controls (52 postmenopausal women and 47 men). Type 2 diabetes mellitus patients were selected consecutively from the outpatient Endocrinology Service of Cumhuriyet University Hospital, Sivas, Turkey from April 2002 to March 2005. We collected demographic, leptin, insulin resistance, and lipid and body composition parameters.

Results: Serum leptin levels of females were significantly higher than those of men in both T2DM, and healthy participants. The basal metabolic rate, fat free mass, and total body water of males, were lower than those of females. In both T2DM and healthy participants, leptin was positively correlated with insulin resistance and body composition parameters in both gender. Serum leptin levels of females were higher compared with males in the same BMI, independent of T2DM.

Conclusion: Leptin was associated with insulin, insulin resistance, and body composition parameters (body mass index, basal metabolic rate, body weight, %fat, and fat mass) in participants, with or without T2DM in both genders. Type 2 diabetes mellitus seemed more effective on insulin resistance than obesity. We suggest that the female gender, and fat mass, and not T2DM might have significant influence on leptin levels in age.

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Leptin plays a critical role in the regulation of body weight by inhibiting food intake, and stimulating energy expenditure. In humans, the circulating leptin level is increased in obesity, and is positively correlated with the total body fat mass. Leptin is one of the adipokines regulating insulin sensitivity.[1,2] Diabetes currently affects an estimated 171 million individuals worldwide.[3] Type 2 diabetes mellitus (T2DM) is approaching epidemic proportions, mostly due to a sharp increase in the prevalence of obesity, and associated insulin resistance.[4] Being overweight or obese has become highly prevalent, and is rapidly reaching epidemic proportions in the developing world.[5] There is evidence for a causal link between obesity and T2DM. Obesity, one of the basic causes of T2DM, worsens insulin resistance, although the pathophysiological mechanisms remain uncertain.[6] An increase and redistribution of body fat during menopause predisposes women to cardiovascular disease and clinical disorders, including obesity, insulin resistance, glucose intolerance, and dyslipidemia (hypertriglyceridemia and low-high density lipoprotein cholesterol levels).[7] A previous study has shown a correlation of body mass index (BMI) with insulin and leptin levels in postmenopausal women.[8] The aim of this study was to investigate the association of leptin with insulin resistance (IR), body composition, and serum fasting lipid parameters in postmenopausal women and men with T2DM.

Methods. Patients with T2DM were selected consecutively from the outpatient Endocrinology Service of Cumhuriyet University Hospital, Sivas, Turkey in April 2002 until the end of March 2005. In the study, 158 diabetic patients (87 women at menopausal age and 71 men at age) were enrolled as the type 2 diabetic group. In the control group, 100 healthy controls (52 women at menopausal age and 47 men) were recruited either by hospital staff, or from those who came for annual physical check-up. The Human Ethics Committee approved the study, and each subject signed an informed consent. Inclusion criteria were T2DM, as defined by the clinical criteria of the American Diabetes Association, at least for one year, age 40-75 years old, and being postmenopausal for female subjects.[9] Exclusion criteria were: proliferative retinopathy, pregnancy or lactation, ketoacidosis, renal failure (serum creatinine >1.5 mg/dL), thyroid diseases, liver disease, or recent history of cardiovascular disease, and alcoholism, or other serious diseases. Subjects taking drugs known to affect lipoprotein oxidation (namely, vitamin E, vitamin C, or probucol), hormone replacement therapy for postmenopausal women, and anti lipidemic agents were excluded from the study. Menopause was defined as being amenorrheic at least one year. All patients with T2DM were treated with metformin in doses varying from 500 mg to 3000 mg/day, or the combination therapy of metformin (n=32), plus sulphonylurea (glibenclamide 2.5-10 mg/day or glipizide 2.5-20 mg/day). Thirty-five subjects in the type 2 diabetic group were on antihypertensive treatment. Body composition was determined by conventional bioelectrical impedance analysis (BIA) in the morning after an overnight, at least 10 hours fast, and then blood was collected from all subjects.

Body composition measurements. Body composition was determined by BIA. A single investigator with a single-frequency 50-kilohertz bioelectrical impedance analyzer, according to the standard tetrapolar technique, measured resistance, and reactance. Before each testing session, the external calibration of the instrument was checked with a calibration circuit of known impedance value. The mean coefficient of variation was 1% for within the day, and 3% for weekly intra-individual measurements in the steady state condition in either site, and 2% for inter-operator variability. Bioelectrical impedance measurements were taken by using the Tanita Body Fat Analyzer (model TBF 300, Tanita Corporation of America Inc, IL, USA) in the morning, after overnight fasting, and after voiding. Subjects were measured while standing erect, on bare feet, on the analyzer's footpads, and wearing either a swimsuit or undergarments. The 4 electrodes of the system were in the form of stainless steel footpads, mounted on the top surface of a platform scale. Each footpad was divided in half so that the anterior and posterior portions form 2 separate electrodes. Current was applied via the anterior portion of the footpad electrodes, and then the voltage drop across the posterior (heel) electrodes was measured.[13] Leg-to-leg impedance, and body mass were simultaneously measured, as the subject's bare feet make pressure contact with the electrodes and digital scale. Fat-free mass was calculated by using the prediction equations supplied by the manufacturer by using weight, age, and an impedance index, height^2/Z, and percentage body fat was estimated by using the equation of Brozek et al.[12] Body composition was calculated from bioelectrical measurements and anthropometric data by applying the software provided by the manufacturer, which incorporated validated predictive equations for total body water (TBW), BMI, basal metabolic rate (BMR), fat mass (FM), percent fat (%fat), and fat-free-mass (FFM).[13,14] Before testing, subjects were required to adhere to these BIA testing guidelines: 1) not to eat or drink within 5 hours of the test, 2) to maintain normal body hydration, 3) not to consume caffeine and alcohol within 12 hours of the test, 4) not to exercise within 12 hours of the test, 5) not to take diuretics within 7 days of the test, and 6) not to urinate within 30 minutes of

the test.[15] Body mass was determined using a physician's balance-beam scale, and the height was measured using a stadiometer.

Serum leptin and insulin measurements. Fasting serum leptin concentrations were measured with a human leptin radioimmunoassay (125I human leptin, Linco Research, MO, USA) according to manufacturer's recommendations. It is a homologous assay with the antibody being raised against highly purified human leptin, and both standard and tracer being prepared with human leptin. The coefficients of variation ranged from 3.4-8.3% (within-run), and between 3.6-6.2% (between-run). Serum insulin and C-peptide were measured using a 2-site immunoenzymometric assay (mean intra-CV was 1.7%, and interassay CVs was 3.3%) (Diagnostic Products Corporation, Los Angeles, CA, USA).[10] Serum glucose (reference range, 3.8-5.8 mmol/mL) was determined by hexokinase method in an ILab 900/1800 automatic analyzer (Instrumentation Laboratories, Lexington, MA, USA).[11] The glycosylated hemoglobin (HbA1c) was measured by the method of turbidimetric inhibition immunoassay using Tina/quant HA1c II kit (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). According to the reference values of HbA1c for the Tina-quant HbA1c assay, the normal range was 4.8-6%.[11]

Homeostasis model assessment calculation. Insulin resistance (HOMA-IR) and ß-cell function (HOMA-ß) were assessed by homeostasis model assessment (HOMA) using fasting serum insulin, and blood glucose.[12] Insulin resistance HOMA-IR=fasting insulin (mIU/L) x fasting glucose (mmol/L)/22.5, and HOMA-ß=20 x ß fasting insulin (mIU/L)/fasting glucose (mmol/L)-3.5.

Blood sampling and laboratory method. Blood was collected in the morning after an overnight, at least 10 hours fast. Samples were sent for analysis of fasting serum lipids (triglyceride (TG), cholesterol, high-density lipoprotein cholesterol (HDL-C), low- density lipoprotein cholesterol (LDL-C), and very low- density lipoprotein cholesterol (VLDL-C), and measurements of fasting serum glucose, leptin, insulin, HbA1c, creatinine, and C-peptide concentrations. Serum TG levels (reference range 40-160 mg/dL), cholesterol (reference range, 140-220 mg/dL) was determined by enzymatic colorimetric methods.[16] High-density lipoprotein-cholesterol was measured by standard enzymatic methods on a centrifugal analyzer (Multistat III Plus, Instrumentation Laboratory, Lexington, MA, USA). Low-density lipoprotein-cholesterol levels (reference range 80-190 mg/dL) were calculated by the Friedewald formula.[17] Very low-density lipoprotein-cholesterol was estimated by dividing the TG levels by a factor of 5. Blood samples were taken on days 5-7 of the menstrual cycle in women. Free triiodothyronine (T3) (reference range, 1.4-4.4 pg/mL), free thyroxine (T4) (reference range, 0.7-1.8 ng/mL), and ultrasensitive tyroid stimulating hormone (hTSH) II (reference range, 0.4-4.7 µIU/mL) were evaluated by commercial RIA (Abbott Laboratories, Abbott Park, IL, USA) in an AxSYM immunoassay automatic analyzer. Serum creatinine levels (reference range, 0.6-1.3 mg/dL) were determined by colorimetric methods (Instrumentation Laboratories, Lexington, USA).

Statistical analysis. Sample size calculation for patients and healthy controls was performed separately. By considering a standard deviation (SD) for leptin levels of 7.5 ng/mL, 155 patients were required to detect

Table 1 - Selected clinical and laboratory data of study subject, median (maximum-minimum).

Characteristics	Postmenopausal women		Men	
	Controls (n=52)	Type 2 diabetic group (n=87)	Controls (n=47)	Type 2 diabetic group (n=71)
Age (years)	52.0 (40.0-75.0)	56 (41.0-74.0)	51.0 (42.0-75.0)	56.5 (41.0-75.0)
Duration of diabetes (month)	-	108 (17.0-360.0)	-	117 (12.0-240.0)
Duration of diabetes treatment (month)	-	36 (9.0-240.0)	-	32 (8.0-240.0)
History of familial diabetes n (%)	6 (11.5)	43 (49.4)	5 (10.6)	28 (39.4)
Familial obesity n (%)	12 (23.1)	34 (39.0)	10 (21.2)	30 (42.2)
Hypertension n (%)	5 (9.6)	29 (33.3)	3 (6.4)	17 (23.9)
Free T3 (pg/mL)	1.9 (1.6-3.3)	2.2 (1.6-3.4)	1.9 (1.5-2.5)	2.3 (1.0-3.5)
Free T4 (ng/mL)	1.1 (0.8-1.7)	1.1 (0.7-1.6)	1.2 (0.9-1.7)	1.2 (0.8-1.6)
Ultrasensitive hTSH (µIU/mL)	1.8 (1.6-3.1)	1.2 (0.6-3.2)	1.2 (0.9-3.0)	1.2 (0.7-2.7)
Creatinine (mg/dL)	1.0 (0.9-1.4)	1.0 (0.8-1.5)	1.2 (1.0-1.4)	1.2 (0.5-1.5)

T3 - tri-iodothyronine, T4 - thyroxine, hTSH - tyroid stimulating hormone

Table 2 - Leptin level and insulin resistance parameters, median (minimum-maximum).

Parameters	Postmenopausal women		Men	
	Controls (n=52)	Type 2 diabetic group (n=87)	Controls (n=47)	Type 2 diabetic group (n=71)
Leptin (ng/mL)	29.3 (7.5-55.4)*	30.1 (2.3-116.0)†	8.8 (0.5-20.5)	8.7 (0.4-20.6)
Insulin (µIU/mL)	4.0 (2.0-12.1)	9.4 (2.0-70.6)‡	4.1 (2.0-19.5)	7.7 (2.0-47.2)
HOMA-IR	0.9 (0.4-2.8)	3.9 (0.5-40.3)‡	0.9 (0.3-4.1)	2.3 (0.4-30.1)*
HOMA-ß	53.3 (20.0-202.5)	31.4 (1.7-705.2)‡	48.6 (14.1-319.1)	20.3 (2.8-267.1)*
Fasting glucose (mg/dL)	92 (75.0-123.0)	159.0 (75.0-478.0)‡	91.0 (62.0-118.0)	167.5 (82.0-377.0)*
HbA1c (%)	5.8 (4.8-6.0)	7.7 (3.3-15.6)‡	5.2 (4,8-5,9)	9.1 (3.6-15.3)*
C-peptide (ng/ml)	5.2 (0.7-12.8)	3.9 (0.5-10.6)	3.5 (0.6-8.8)	3.3 (0.5-14.0)

HOMA-IR - insulin resistance, HOMA-β - β-cell function, *p=0.00 versus male controls, †p=0.01 versus male type 2 diabetic group, ‡p=0.02 versus female controls

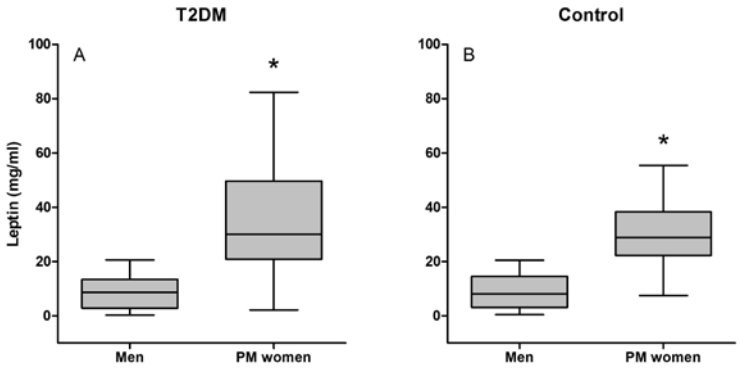

Figure 1 - The leptin levels in diabetic and healthy postmenopausal women and men. *p=0.00 versus men in both **A**) diabetic, and **B**) control groups. PM - postmenopausal, T2DM - type 2 diabetes mellitus.

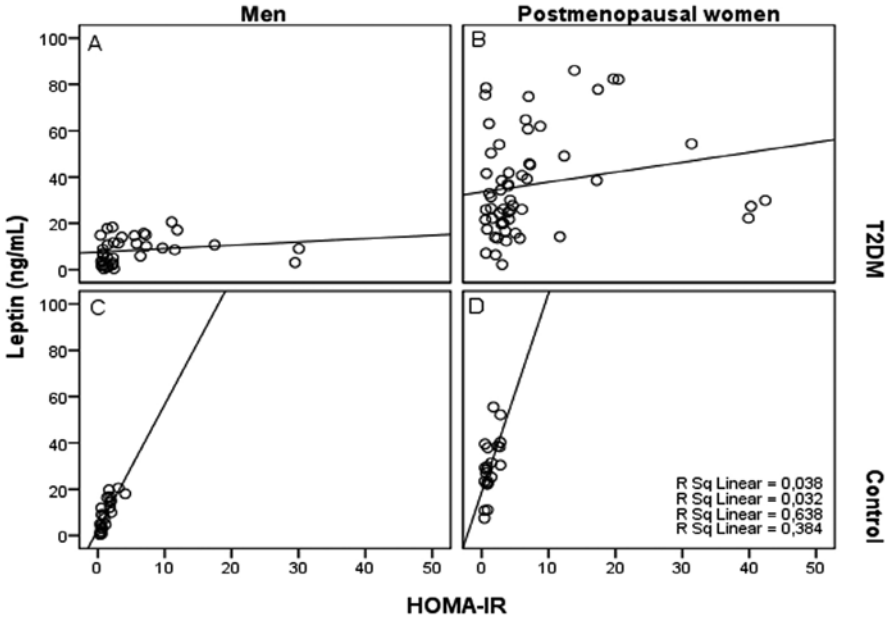

Figure 2 - The correlation between leptin and insulin resistance (HOMA-IR) in **A** & **B**) type 2 diabetes mellitus (T2DM) and **C** & **D**) healthy postmenopausal women and men.

a mean difference of 15 ng/mL with 95% confidence level, and 90% power. All 98 healthy controls were required to detect the difference in mean leptin level of 15 ng/mL, with SD of 6 ng/mL. We included 163 patients (87 postmenopausal women and 71 men) with T2DM, and 103 healthy controls (52 postmenopausal women and 47 men), which is 5% more than the calculated sample size. Data were presented as median (minimum-maximum), and percentages. Serum leptin level and insulin resistance parameters, and lipid and body composition parameters, for both female and male subjects in type 2 diabetic group and controls, were analyzed with Mann-Whitney U test. In both female and male subjects of type 2 diabetic group, Spearman correlation coefficients, and multiple regression analysis were calculated between leptin level and insulin, fasting glucose, and C-peptide levels, HOMA-IR, HOMA-ß, and HbA1c values, BMI, BMR, BW, %fat, FM, FFM, TBW, and serum fasting lipid levels. We considered $p<0.05$ as statistically significant.

Table 3 - Lipid and body composition parameters, median (minimum-maximum).

Parameters	Postmenopausal women		Men	
	Controls (n=52)	Type 2 diabetic group (n=87)	Controls (n=47)	Type 2 diabetic group (n=71)
BMI (kg/m²)	29.2 (23.1-43.2)	29.0 (19.5-53.5)	27.8 (20.6-34.1)	28.4 (22.0-36.8)
BMR (kcal)	1363.0 (1218.0-1812.0)*	1352.0 (1019.0-1951.0)†	1641.0 (1075.0-1885.0)	1490.0 (1013.0-2042.0)
BW (kg)	71.9 (53.3-111.1)	69.7 (43.9-128.5)	73.3 (49.9-90.4)	67.8 (46.6-106.7)
%Fat	35.4 (20.7-47.6)*	37.2 (15.7-52.5)†	22.3 (8.6-28.4)	18.8 (5.2-32.7)
FM (kg)	26.1 (11.0-52.9)*	25.2 (5.4-67.5)†	15.2 (4.3-24.8)	12.2 (2.5-33.2)
FFM (kg)	45.6 (40.0-58.2)*	45.6 (35.6-61.0)†	57.6 (45.4-65.8)	54.4 (37.7-81.9)
TBW (kg)	33.4 (29.3-42.6)*	34.0 (26.1-44.7)†	42.2 (33.2-48.2)	39.9 (27.6-60.0)
Fasting lipids (mg/dl)				
Cholesterol	211.0 (138-279.0)*	196.0 (98.0-413.0)†	180.0 (121.0-229.0)	181.0 (92.0-369.0)
Triglyceride	129.0 (79.0-228.0)	184.5 (55.0-859.0)†‡	120.0 (81.0-345.0)	133.0 (61.0-504.0)
HDL-C	45.0 (28.0-179.0)	39.0 (21.0-78.0)‡	43.0 (31.0-61.0)	37.0 (16.0-82.0)*
LDL-C	122.0 (55.0-195.0)	115.5 (44.0-240.0)	114.0 (66.0-152.0)	112.0 (39.0-233.0)
VLDL-C	27.5 (19.0-46.0)	37.0 (12.0-172.0)†‡	24.0 (17.0-69.0)	27.0 (12.0-101.0)

BMI - body mass index, BMR - basal metabolic rate, TBW - total body water, BW - body weight, FM - fat mass, %Fat - percent fat, FFM - fat-free-mass, HDL-C - high-density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol, VLDL-C - very low- density lipoprotein cholesterol,
*p=0.02 versus male controls, †p=0.02 versus male type 2 diabetic group, ‡p=0.01 versus female controls

Table 4 - Correlation of leptin and insulin levels, insulin resistance, lipid, and body composition parameters.

Parameters	Postmenopausal women				Men			
	Controls (n=52)		Type 2 diabetic group (n=87)		Controls (n=47)		Type 2 diabetic group (n=71)	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Insulin (mlU/mL)	0.7	0.00	0.4	0.01	0.8	0.00	0.4	0.01
HOMA-IR	0.7	0.00	0.3	0.02	0.8	0.00	0.4	0.01
HOMA-β	0.5	0.00	0.3	0.02	0.7	0.00	0.4	0.01
Fasting glucose (mg/dL)	0.2	>0.05	-0.2	>0.05	0.1	>0.05	-0.1	>0.05
BMI (kg/m²)	0.5	0.01	0.4	0.01	0.6	0.00	0.4	0.01
BMR (kcal)	0.5	0.01	0.4	0.01	0.8	0.00	0.5	0.00
BW (kg)	0.5	0.00	0.5	0.01	0.9	0.00	0.7	0.00
%Fat	0.6	0.00	0.4	0.01	0.8	0.00	0.6	0.00
FM (kg)	0.5	0.01	0.5	0.01	0.9	0.00	0.7	0.00
FFM (kg)	0.2	>0.05	0.2	>0.05	0.8	0.00	0.5	0.01
TBW (kg)	0.2	>0.05	0.2	>0.05	0.8	0.00	0.5	0.00

HOMA-IR - insulin resistance, HOMA-β – β-cell function,
BMI - body mass index, BMR - basal metabolic rate, TBW - total body water, BW - body weight,
FM - fat mass, %Fat - percent fat, FFM - fat-free-mass,

Table 5 - Multiple regression analysis of factors affecting serum leptin levels.

Independent Variables	Coefficients	*P*-value
Gender (n)	0.30	0.006
T2DM (n)	-0.01	ns
Obesity (n)	0.01	ns
insulin (µIU/mL)	0.24	0.000
BW (kg)	0.49	0.001
Familial obesity (n)	0.12	ns
Hypertension (n)	0.06	ns
FFM (kg)	-0.29	ns
Triglyceride (mg/dl)	0.02	ns
Cholesterol (mg/dl)	0.10	ns

T2DM - type 2 diabetes mellitus, FFM - fat-free-mass, BW -body weight, ns - non significant

Results. In this study, 163 patients were recruited and 5 patients were excluded. One hundred and three healthy controls were recruited and 4 controls were excluded. In both female and male subjects, there were no significant differences in age, duration of diabetes, duration of diabetes treatment, history of familial diabetes, familial obesity, tri-iodothyronine, thyroxine, hTSH, and creatinine levels between the study groups (**Table 1**). **Table 2** presents leptin levels and insulin resistance parameters (insulin, HOMA-IR, HOMA-ß, fasting glucose, HbA1c, C-peptide). In both postmenopausal women and men groups, we found no significant differences in leptin levels between type 2 diabetic group and controlled ($p>0.05$). Leptin levels of both type 2 diabetic and controls in the postmenopausal women group, were significantly higher than those of type 2 diabetic and controls in the male group (**Figure 1a** & **1b**). Insulin, HOMA-IR, fasting glucose levels, and HbA1c of type 2 diabetic patients were significantly higher than those of controls in postmenopausal women group. ß-cell function of type 2 diabetic patients was significantly lower than those of controls in postmenopausal women group. Insulin resistance, fasting glucose levels, and HbA1c of type 2 diabetic patients, were significantly higher than those of the control in men group. ß-cell function of type 2 diabetic patients, was significantly lower than those of controls in postmenopausal women group. **Table 3** presents body composition parameters (BMI, BMR, BW, %fat, FM, FFM and TBW), and serum fasting lipids (cholesterol, TG, HDL-C, LDL-C, and VLDL-C). The BMI and BW values of diabetic patients and controls in both postmenopausal women and men groups were similar. In postmenopausal women, the values of BMR, FFM and TBW in diabetic patients and controls were significantly lower than those of men. In postmenopausal women, the values of %fat and FM in diabetic patients and controls, were significantly higher than those of men. In postmenopausal women, the values of cholesterol in diabetic patients and controls were significantly higher than those of men. Triglycerides and VLDL-C levels of diabetic patients were significantly higher than those of both controls in postmenopausal women and diabetic patients in men. High density-lipoprotein cholesterol levels of diabetic patients is significantly lower than those of controls, in both postmenopausal women and men. In controls of postmenopausal women group, there were statistically significant, moderate positive correlations between leptin and insulin, HOMA-IR, HOMA-ß, BMI, BMR, BW, %fat, FM, and cholesterol level (**Table 4** and **Figure 2C & 2D**). In diabetic patients of the postmenopausal women group, our study showed moderate positive correlations between leptin and insulin, BMI, BMR, BW, %fat, and FM, and displayed low positive correlations between leptin and HOMA-IR, and HOMA-ß (**Figure 2A & 2B**). In the controls of men group, we found statistically significant, strong positive correlation between leptin and insulin, HOMA-IR, BMR, BW, %fat, FM, FFM, and TBW, and statistically significant moderate positive correlations between leptin and HOMA-ß, BMI, cholesterol, TG, and VLDL-C. In diabetic patients of the male group, we found moderate positive correlations between leptin and insulin, HOMA-IR, HOMA-ß, C-peptide, BMI, BMR, BW, %fat, FM, FFM, TBW TG, and VLDL-C. In the male diabetic patients group, we observed low negative correlation between leptin and HDL-C. **Table 5** shows multiple regression analysis of factors affecting serum leptin levels. There was a good correlation between serum leptin levels with gender, %fat, insulin, HOMA-IR, BW, BMI, FM whereas no correlation was observed with T2DM, obesity, familial obesity, hypertension, FFM, TBW, triglyceride, VLDL, and cholesterol. There was no correlation between fasting blood glucose and leptin levels.

Discussion. We found no effect of T2DM on serum leptin levels in both female and male subjects, however, we observed 3 times higher leptin levels in postmenopausal women than men. Leptin was moderately correlated with several measures of insulin resistance parameters and body composition parameters in both female and male participants. There was a correlation between leptin and FFM, TBW, TG, and VLDL-C levels in men, while no correlation was found in postmenopausal women.

Type 2 diabetes mellitus is a complex metabolic disease, which accounts for 90% of all patients with

diabetes.[9] Leptin level was lower in women with T2DM, than in women without T2DM, similar with the findings of previous studies.[18,19] Leptin level was correlated with BMI in women with and without T2DM. Contrary to these findings, we found no significant change in leptin levels of subjects with or without diabetes as in the study, however, leptin level was generally positively correlated with BMI and body composition parameters in our study.[19] Logically, the relationship between leptin and insulin sensitivity may not be causal, however, it may be related to fat mass, as leptin concentrations are proportional to fat mass, and obesity causes insulin resistance.[20] Although both genders of type 2 diabetic and healthy subjects had similar BW, leptin and body composition parameters were higher in female participants in our study. It may be a result of leptin resistance in overweight women.

The daily energy expenditure includes the energy to support our BMR and our physical activity, and the energy required to process the food.[21] The BMR is usually lower for women than for men of the same weight, as women usually have more metabolically inactive adipose tissue. According to our findings, BMR was lower for women than for men of the same body weight, and BMI. We also found that leptin level was correlated with BMR in both postmenopausal women and men, with or without T2DM. However, no significant correlation between BMR and fasting plasma leptin concentration was found.[22]

The most accurate decision rule was based on HOMA-IR and BMI: declare an individual to be test positive if HOMA-IR >4.65, or if HOMA-IR >3.6, and BMI >27.5 kg/m^2; otherwise, declare that individual to be test negative.[23] In accordance with those findings, the HOMA-IR values were positive in diabetic patients in both genders, whereas they were negative in healthy participants in our study. Thus, we concluded that diabetes mellitus was a primary factor in the determination of HOMA-IR rather than being overweight, as in healthy participants.

Insulin resistance was hypothesized to play a major role in dyslipidemia in T2DM.[24,25] It was reported as elevated triglycerides, and LDL cholesterol, and low levels of HDL cholesterol in obese adults.[14,26] However, in some studies, similar lipid profiles have been reported in obese and nonobese adults with T2DM, in obese normoglycemic adults, and in nonobese adults with impaired glucose tolerance.[27] Among patients with T2DM, insulin resistance and obesity are associated with hypertriglyceridemia, low serum HDL-C concentrations, and occasionally high serum LDL-C.[24,28] Several mechanisms whereby insulin resistance could cause an alteration in lipid metabolism have been described. Hyperinsulinemia is known to enhance hepatic VLDL-C synthesis, and thus may directly contribute to the increased plasma triglyceride and LDL-C.[29] It has been suggested that insulin resistance may be responsible for the reduced levels of HDL cholesterol observed in T2DM, despite enhanced HDL cholesterol synthesis.[30] Our findings suggest that T2DM, and high body composition parameters cause more deterioration in cholesterol, TG, VLDL-C, and HDL-C levels, and, not in LDL-C level in postmenopausal women. In our study, leptin levels of male participants, with or without diabetes, showed correlation with TG and VLDL-C. Obesity in postmenopausal women results in elevations in adipocytokines, which increase the prevalence of insulin resistance.[7] It was found that BMI largely explains the characteristic relationship of elevated triglycerides, and lower HDL-C in IR, and obesity is principally responsible for the IR of postmenopausal women. It also demonstrated that, while adipocytokine values as leptin are abnormal, these factors are predominantly influenced by BMI, and may accentuate IR, particularly in the case of elevated leptin levels. In our study, we also found that lipid parameters in diabetic participants in postmenopausal women were similar in the previous study, however, leptin levels were predominantly influenced by gender and not diabetes mellitus.

One of the limitations of this study was that, we did not study normal-weight postmenopausal women and men, for comparisons of leptin levels. Another limitation was that, we did not have premenopausal women and younger men groups, as control. However, our purpose here was not to focus on differences in leptin levels between postmenopausal women and men, and younger population, likewise to assess leptin, and its relationship to diabetes mellitus in a selected group of both gender.

In conclusion, the serum leptin level of postmenopausal women was increased, compared with men in the same BMI independent of diabetes mellitus. Leptin was associated with IR and body composition parameters in both genders in overweight people. Diabetes mellitus was more effective on IR than obesity. Leptin had been correlated with triglyceride and VLDL cholesterol levels in only the male population, with or without T2DM. The female gender and fat mass, and not T2DM have a meaningful influence on leptin levels in age in overweight people. Comparisons of leptin and IR parameters in pre- and postmenopausal women and men, in various ages might be the focus of future studies.

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