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Serum Leptin Levels in Patients with Type 2 Diabetes Mellitus, First Degree Relatives of Diabetic Patients, Prediabetes, Correlation with Carotid Intima Media Thickness.

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ABSTRACT

Background: *Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia due to insulin resistance and inadequate secretion, leading to complications. Obesity exacerbates these risks, with leptin implicated in body weight regulation and cardiovascular disease (CVD). Carotid intima-media thickness (CIMT) serves as a noninvasive marker of preclinical atherosclerosis.*

Aim: *To assess serum level of leptin as adibocytokine in patient with type 2 diabetes mellitus, first degree relatives of diabetic patients, prediabetes and control subject and detect its relation to carotid IMT as a measure of preclinical atherosclerosis.*

Patients and methods: *The study included 100 subjects from Internal Medicine Insurance clinics and diabetes & endocrinology unit outpatient clinic in Beni-Suef University hospital from January 2017 until March 2018. They were divided into four groups: Type 2 DM group: twenty-five patients with type 2 diabetes. Prediabetes group: twenty-five. Relatives of diabetic group: twenty-five subjects first degree relative of type 2 diabetic patients. Normal controls group: twenty-five of normal volunteers*

Results: *Leptin levels were significantly higher in T2DM (34±10 ng/ml) and prediabetes (29.6±14.9 ng/ml) vs. relatives (14±6 ng/ml; $p<0.05$), with females showing elevated levels. CIMT was increased in T2DM (0.81±0.17 mm) and prediabetes (0.71±0.12 mm) vs. relatives (0.45±0.05 mm) and controls (0.62±0.13 mm; $p<0.05$). Leptin correlated positively with CIMT ($r=0.258$, $p=0.010$) and other risk factors. At 15 ng/ml cutoff, leptin predicted increased CIMT (sensitivity 81.5%, specificity 66%; $p=0.028$).*

Conclusion: *Elevated leptin is associated with increased CIMT in T2DM and prediabetes, indicating accelerated atherosclerosis. CIMT monitoring aids risk assessment; relatives show lower risk.*

Keywords: *Type 2 Diabetes Mellitus, Leptin, Carotid Intima Media Thickness*

INTRODUCTION

Type 2 diabetes mellitus consists of dysfunctions characterized by hyperglycaemia and resulting from the combination of resistance to insulin action, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Poorly controlled type 2 diabetes is associated with an array of micro vascular and macro vascular complications (1).

Micro vascular complications of diabetes include retinal, renal, and possibly neuropathic disease. Macro vascular complications include coronary artery and peripheral vascular disease. Diabetic neuropathy affects autonomic and peripheral nerves (2).

Obesity is a pandemic medical and social problem that is associated with several adverse health outcomes, including metabolic related diseases such as T2DM, cardiovascular diseases, dyslipidemia, hypertension and bone fragility as well as non-metabolic derangements such as non-alcoholic fatty liver disease, polycystic ovary syndrome, neoplasias and glomerulopathy, among others, all of which result in increased mortality (3).

The obese (Ob), or leptin (LEP) gene whose name is derived from the Greek (leptos) stands for "thin", it was first cloned in 1994 and it encodes the release of leptin hormone (4).

Leptin is a circulating 16 KDa peptide hormone, its similar in structure to cytokines of the long-chain helical family that includes interleukin (IL)-6, IL-11, IL-12, and oncostatin M, making it a part of the adipokines family (5).

Leptin has an important role in the long-term regulation of body weight. It has also been proposed as an independent risk factor for CVD and as an important link between obesity and cardiovascular risk (6).

Because cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, the potential value of a non-invasive imaging method that allowed direct visualization of the arterial wall and provided quantification of all stages of the athero-sclerotic process was great. Previously, while ultrasound was widely employed as a screening tool for carotid disease, the B-mode image of the vessel was used as an adjunct to obtaining accurate doppler flow measurements from the site of maximum lumen narrowing. The vessel wall was largely ignored, since the focus was on identifying patients with high-grade stenosis who might be candidates for carotid endartectomy (7).

Our study aimed to assess serum level of leptin as adibocytokine in patient with type 2 diabetes mellitus, first degree relatives of diabetic patients, prediabetes and control subject and detect its relation to carotid IMT as a measure of preclinical atherosclerosis.

SUBJECTS AND METHODS

The study included 100 subjects recruited from Internal Medicine Insurance clinics and diabetes & endocrinology unit outpatient clinic in Beni-Suef University hospital in the period from January 2017 until March 2018. They were divided into **four groups: Type 2 DM group:** twenty-five patients with type 2 diabetes diagnosed according to American Diabetes Association 2013. **Prediabetes group:** twenty-five diagnosed according to American Diabetes Association 2013. **Relatives of diabetic group:** twenty-five subjects first degree relative of type 2 diabetic patients. **Normal controls group:** twenty-five of normal volunteers

Inclusion criteria: Diabetes mellitus duration more than 10 years, prediabetic, first degree relatives of patients with type 2 diabetes mellitus.

Exclusion criteria: H C V infection, history of previous cerebrovascular stroke, type 1 diabetes mellitus and renal impairment (serum creatinine> 1.3 mg/dL for men and > 1.1 mg/dL for women).

Methods

All patients were subjected to the following:

Complete history taking: including age, diabetes duration, smoking, medication use, history of cardiac and cerebrovascular symptoms and physical examinations: including measurement of blood pressure in the sitting position after at least 5 minutes of rest, weight and height, BMI was calculated from weight (kg) height (m) ^{2}, waist circumference.

Laboratory assessment, including: Serum creatinine, Blood Urea Nitrogen (BUN), H C V antibody by ELISA and fasting blood glucose, 2hours postprandial glucose (2h PG), HbAlc, Albumin / Creatinine ratio (spot) and Lipid profile. Total cholesterol, Serum triglycerides, High density lipoprotein cholesterol, Low density Lipoprotein cholesterol and **plasma leptin level:** The DRG Leptin Sandwich ELISA is an enzyme immunoassay for the quantitative in vitro diagnostic measurement of Leptin in serum. The DRG Leptin Sandwich ELISA is a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. The microtiter wells are coated with a monoclonal antibody directed towards a unique antigenic site on a Leptin molecule. An aliquot of patient sample containing endogenous Leptin is incubated in the coated well with a specific biotinylated monoclonal anti-Leptin antibody. A sandwich complex is formed. After incubation the unbound material is washed off and a Streptavidin Peroxidase Enzyme Complex is added for detection of the bound Leptin. Having added the substrate solution, the intensity of color developed is proportional to the concentration of Leptin in the patient sample.

Specimen Collection: Peripheral venous blood samples (5ml) were collected from the patients and healthy subjects at the time of registration for the study. To prepare serum, whole blood was directly drowned in a vacutainer serum tube that contain no anticoagulant. Let blood clot at room temperature for 30 minutes. Promptly centrifuge the clotted blood at 2000 to 3000 x.g. for 15 minutes at 4±2°C. Transfere and store serum sample in a separate tube, date and identify.

Assessment of intima media thickness by carotid artery duplex: CIMT is a noninvasive test which is performed with a high-resolution B-mode ultrasound transducer logic S6 Supplied by GE health care America in radiology department in faculty of medicine BeniSueif University.

The reference limits of CIMT according to the age classes 18-29, 30-39, 40-49 and 50-59 years were estimated as 0.47, 0.59, 0.67 and 0.70 mm in women and 0.47, 0.62, 0.72 and 0.80 mm in men

(Randrianarisoa et al.,2015).

Statistical analysis

Analysis of data was performed using SPSS version 22 (Statistical Package for Social science) for Windows. Description of variables was presented as follows: in the form of mean, standard deviation (SD), minimum and maximum for quantitative variables and in the form of numbers (No.) and percent's (%) for qualitative variables. Comparison between quantitative variables was carried out by one way ANOVA test which was used to test the difference between the means of several subgroups of a variable (multiple testing). Comparison between categorical data was done using the Chi square test, to test the statistical difference between the two groups. ROC was used to predict the sensitivity and specificity of leptin in prediction of increased CIMT. Regression was used to examine the predictor factors that may affect the leptin level. Pearson correlation was used to test the correlation between different quantitative variables. Significant when P-value ≤ 0.05.

RESULTS

Table (1): Gender distribution among the four groups under the study:

Gender	Groups				P-value
	Type 2 DM group NO.25	Relatives of diabetic group NO.25	Prediabetes group NO.25	control group NO.25	
Male	8	11	11	16	0.146
	32.0%	44.0%	44.0%	64.0%	
Female	17	14	14	9	
	68.0%	56.0%	56.0%	36.0%	

Data presented as number and percent

Table 1 showed that there was no significant statistical difference between the four groups regarding their gender distribution (P-value=0.146).

Table (2): Base line characteristics of the study groups:

characteristics		Mean	SD	P-value
Age years	Type 2 DM group	52.2	4.9	P1=0.089 P2=0.349 P3=0.078 P4=0.067 P5=0.052 P6=0.058
	Relatives of diabetic group	47	5.6	
	Prediabetes group	48.9	6.7	
	control group	44	9.2	
Duration of diabetes (years)	Type 2 DM group	12.8	2.7	<0.01*
	Prediabetes group	1.7	0.85	
SBP mm Hg	Type 2 DM group	143.8	14.3	P1<0.01* P2=0.997
	Relatives of diabetic group	117.6	5.2	
	Prediabetes group	143	18.4	
	control group	128	14.5	

				P3=0.044* P4<0.01* P5=0.065 P6=0.013*
DBP mm Hg	Type 2 DM group	87.4	5.6	P1<0.01* P2=0.940 P3=0.045* P4<0.01* P5=0.087 P6=0.030*
	Relatives of diabetic group	78	4.1	
	Prediabetes group	88.4	8.4	
	control group	79	5.9	
BMI	Type 2 DM group	32.3	4.4	P1<0.01* P2=0.455 P3=0.076 P4<0.01* P5=0.099 P6=0.023*
	Relatives of diabetic group	28.1	4.7	
	Prediabetes group	34.3	5.6	
	control group	29.2	4.5	
W.C cm	Type 2 DM group	107.8	10.4	P1<0.01* P2=0.819 P3=0.033* P4<0.01* P5=0.233 P6=0.011*
	Relatives of diabetic group	93	12.4	
	Prediabetes group	110.4	8.9	
	control group	96.4	9.4	

Data was presented as mean and SD *P-value was considered significant at <0.05
P1 (between Type 2 DM and Relatives of diabetic groups)
P2 (between Type 2 DM and Prediabetes groups)
P3 (between Type 2 DM and control groups)
P4 (between Relatives of diabetic and Prediabetes groups)
P5 (between Relatives of diabetic and control groups)
P6 (between Prediabetes and control groups)
Table 2 showed that there was a statistically significant difference between the four groups regarding their base line characteristics (P-value<0.05).

Table (3) Laboratory criteria of all groups under the study:

Laboratory criteria	Mean	SD	P-value

Creatinine mg/dl	Type 2 DM group	0.9	0.12	P1<0.01* P2=0.823 P3=0.523 P4=0.017* P5=0.063 P6=0.958
	Relatives of diabetic group	0.7	0.15	
	Prediabetes group	0.8	0.14	
	Control group	0.8	0.1	
A.C.R mg/g	Type 2 DM group	156.5	20.8	P1=<0.01* P2=0.047* P3=0.004* P4=0.595 P5=0.980 P6=0.823
	Relatives of diabetic group	26	4.6	
	Prediabetes group	68	10.7	
	Control group	29	10	
FBG mg/dl	Type 2 DM group	154.8	43.8	P1<0.01* P2<0.01* P3<0.01* P4<0.01* P5=0.863 P6=<0.01*
	Relatives of diabetic group	81.6	6.1	
	Prediabetes group	116.6	4.3	
	Control group	86.2	7.8	
2h PG mg/dl	Type 2 DM group	267.4	60.9	P1<0.01* P2<0.01* P3<0.01* P4<0.01* P5=0.937 P6<0.01*
	Relatives of diabetic group	118.8	13.5	
	Prediabetes group	179.8	10.9	
	control group	124.1	12.4	
HBA1c	Type 2 DM group	8.7	1.5	P1=<0.01* P2<0.01* P3<0.01* P4<0.01* P5=0.932 P6=0.002*
	Relatives of diabetic group	5.3	0.18	
	Prediabetes group	6.3	0.1	
	Control group	5.4	0.13	

Data was presented as mean and SD *P-value was considered significant at <0.05
P1 (between type 2 DM and relatives of diabetic groups)
P2 (between type 2 DM and prediabetes groups)
P3 (between type 2 DM and control groups)
P4 (between relatives of diabetic and prediabetes groups)
P5 (between relatives of diabetic and control groups)
P6 (between prediabetes and control groups)
Table 3 showed that there was a statistically significant difference between the four groups regarding their laboratory criteria (P-value<0.05).

Table (4): Comparison between all groups as regard leptin and CIMT:

	Mean	SD	P-value

Plasma leptin ng/ml	Type 2 DM group	34	10	P1=0.002* P2=0.821 P3=0.0046 P4=0.033* P5=0.009* P6<0.001
	Relatives of diabetic group	14	6	
	Prediabetes group	29.6	14.9	
	Control group	26	9	
CIMT mm	Type 2 DM group	0.81	0.17	P1<0.001* P2=0.085 P3<0.01* P4<0.01* P5<0.01* P6=0.045*
	Relatives of diabetic group	0.45	0.05	
	Prediabetes group	0.71	0.12	
	Control group	0.62	0.13	

Data was presented as mean and SD *P-value was considered significant at <0.05
P1 (between type 2 DM and relatives of diabetic groups)
P2 (between type 2 DM and prediabetes groups)
P3 (between type 2 DM and control groups)
P4 (between relatives of diabetic and prediabetes groups)
P5 (between Relatives of diabetic and control groups)
P6 (between Prediabetes and control groups)
Table (4) Showed that there was a statistical significant difference between the four groups regarding their plasma leptin level as follow: mean plasma leptin was significantly higher in type 2 DM group than relatives of diabetic group, it was also higher in prediabetes group than relatives of diabetic group and it was higher in control than relatives of diabetic group. (P-value<0.05). There was no statistical significant difference between type 2 DM group & prediabetes group (P-value>0.05). As regard the carotid intima thickness, that of type 2 DM group was significantly higher than relatives of diabetic group and control groups, that of prediabetes was higher than relatives of diabetic group and that of control group was higher than relatives of diabetic group (P-value<0.05). But there was no statistical difference between type 2 DM & prediabetes group (P-value>0.05).

Table (5) comparison between males and females regarding CIMT and leptin in the four groups:

Groups		Gender	N	Mean	Std. Deviation	P-value
Type 2 DM	CIMT mm	Male	8	0.8800	0.18040	0.146
		Female	17	0.7759	0.15207	
	Plasma.leptin ng/ml	Male	8	17.0875	11.95007	0.018*
		Female	17	42.6824	26.89856	
Relatives of diabetic	CIMT mm	Male	11	0.4636	0.06120	0.434
		Female	14	0.4471	0.04232	
	Plasma.leptin ng/ml	Male	11	13.3000	14.03980	0.822
		Female	14	14.8143	18.26004	
Prediabetes	CIMT mm	Male	11	0.7136	0.12002	0.768
		Female	14	0.6993	0.11842	
	Plasma.leptin ng/ml	Male	11	19.1273	11.42428	0.001*
		Female	14	37.9000	12.15718	
Control	CIMT mm	Male	16	0.6069	0.14296	0.625
		Female	9	0.6333	0.09421	
	Plasma.leptin ng/ml	Male	16	18.0081	16.09995	0.002*
		Female	9	42.2111	16.76719	

Table 5 showed that females had high plasma leptin than males in type 2 DM, prediabetic and control groups.

Table (6) correlation between both leptin level and CIMT and different variables in all groups:

		Plasma leptin	CIMT
Age year	Pearson Correlation (r)	0.376	0.775
	P-value	<0.001**	<0.001**
SBP mm Hg	Pearson Correlation (r)	0.251	0.803
	P-value	0.012*	<0.001**
DBP mm Hg	Pearson Correlation (r)	0.202	0.710
	P-value	0.044*	<0.001**
BMI	Pearson Correlation (r)	0.614	0.298
	P-value	0.000**	0.003**
W.C cm	Pearson Correlation (r)	0.559	0.457
	P-value	0.000**	<0.001**
Creatinine mg/dl	Pearson Correlation (r)	0.108	0.468
	P-value	0.285	<0.001**
A.C.R mg/g	Pearson Correlation (r)	0.308	0.384
	P-value	0.002**	<0.001**
FBG mg/dl	Pearson Correlation (r)	0.206	0.633
	P-value	0.040*	<0.001**
2 h PG mg/dl	Pearson Correlation (r)	0.232	0.695
	P-value	0.020*	<0.001**
HBA1c	Pearson Correlation (r)	0.233	0.753
	P-value	0.020*	<0.001**
Cholesterol mg/dl	Pearson Correlation (r)	0.344	0.581
	P-value	<0.001**	<0.001**
TG mg/dl	Pearson Correlation (r)	0.289	0.706
	P-value	0.004**	<0.001**
HDL mg/dl	Pearson Correlation (r)	-0.427	-0.666
	P-value	<0.001**	<0.001**
LDL mg/dl	Pearson Correlation (r)	0.311**	0.719**
Plasma leptin ng/ml	Pearson Correlation (r)		0.258
	P-value		0.010**

**. Correlation is significant at the 0.01 level (2-tailed).*. Correlation is significant at the 0.05 level (2-tailed).

Table 6 showed that in all participants, there was significant linear correlations between plasma leptin and the all-other factors except the creatinine (P-value <0.05). There were significant linear positive correlations between CIMT and all other factors (P-value <0.05).

Table (7): Receiver operating characteristics curve to predict the presence of increased carotid intima media thickness from leptin level

Area Under the Curve				
Test Result Variable(s): Plasma leptin				
Area	SD	P-value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.643	0.055	0.028	0.536	0.751

Table 7 showed that at a cut off (15 ng/ml) of plasma leptin, the presence of increased carotid intima media thickness can be predicted with (81.5%) sensitivity and (66%) specificity (P-value 0.028).

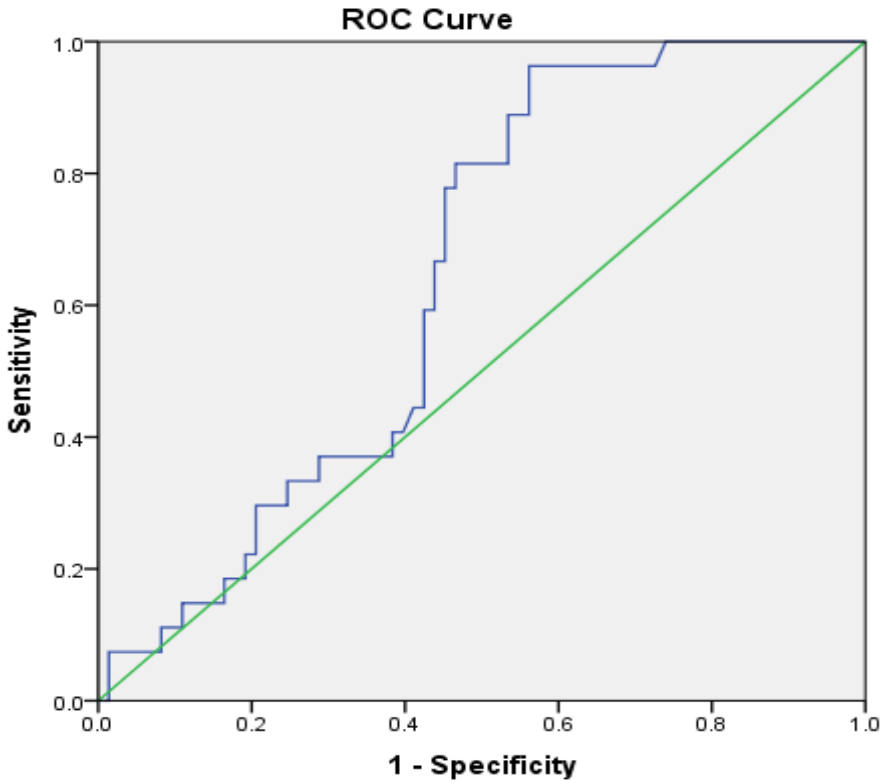

Figure (1) Receiver operating characteristics curve to predict the presence of increased carotid intima media thickness from leptin level

DISCUSSION

Our study showed that there was no significant statistical difference between the four groups regarding their gender distribution (P-value=0.146), there was a statistically significant difference between the four groups regarding their base line characteristics (P-value<0.05), there was a statistically significant difference between the four groups regarding their laboratory criteria (P-value<0.05).

Our study showed that there was a statistical significant difference between the four groups of type 2 DM group, relatives of diabetic group, prediabetes group and normal control group regarding their plasma leptin level as follow: mean plasma leptin was significantly higher in type 2 DM group than relatives of diabetic (34 ± 10 ng/ml) versus (14 ± 6 ng/ml) respectively, it was also higher in prediabetes group than relatives of diabetic (29.6±14.9 ng/ml) versus (14 ± 6 ng/ml) and it was higher in control than relatives of diabetic (26 ± 9 ng/ml) versus (14 ± 6 ng/ml) .(P-value<0.05). Our study showed that females had high plasma leptin than males in type 2 DM, prediabetic and control groups (P-value <0.05).

These finding were in agreement with that of Al-Daghri (8) who found leptin levels of diabetic and pre-diabetic men were higher than in normoglycaemic men (12.4 [3.2–72] vs 3.9 [0.8–20.0] ng/ml). In females, leptin levels were significantly higher in pre-diabetic subjects (14.09 [2.8–44.4] ng/ml) than in normoglycaemic subjects (10.2 [0.25–34.8] ng/ml) (p = 0.046).

We are in agreement with Vavruch et al., (9) their data on leptin in serum were successfully obtained in 246 women and 474 men in the cohort. Women had higher leptin levels ($p < 0.0001$) also when the comparison was corrected for BMI ($p < 0.0001$). There was strong a positive linear relationship between leptin levels and BMI (men: $r = 0.631$, women: $r = 0.667$, both $p < 0.0001$).

As regard our study the carotid intima media thickness, of type 2 DM group (0.81±0.17 mm) was significantly higher than that of relatives of diabetic (0.45±0.05 mm) & control groups (0.62±0.13 mm), and CIMT of prediabetes group (0.71±0.12 mm) was higher than relatives of diabetic group (0.45±0.05 mm) and that of control group (0.62±0.13 mm) was higher than relatives of diabetic group (0.45±0.05 mm) (P-value<0.05). But there was no statistical difference between type 2 DM & prediabetes group (P-value>0.05).

Also these findings are in agreement with Brohall et al., (10) results of twenty-three studies included 24 111 subjects; 4019 with DM and 1110 with IGT. In 20 of 21 studies, the diabetic patients had greater CIMT than the subjects in the control groups.

As regard carotid intema media thickness of our study there was a statistical difference between prediabetic group (0.71±0.12) and control group (0.62±0.13).

In agreement with Bhinder (11) who found that the mean CIMT was higher in prediabetes group in comparison to controls, as the mean value of CIMT in prediabetes (0.79±0.06 mm) was higher than for controls (0.72±0.02 mm). The difference in the two groups was found to be statistically significant (P<0.05). However, was not in abnormal range. According to this model on multiple regression analysis among cases, serum Triglyceride (TG) and age were found to be responsible for increased CIMT.

Our study showed CIMT in relatives of diabetic group (0.45±0.05) was significantly less than type 2 DM (0.81±0.17), prediabetes (0.71±0.12) and control groups (0.62±0.13).

We are in disagreement with Dash (12) who found CIMT were significantly higher in the first degree relatives of type2 diabetes mellitus patients than controls.

Also in contrast to Ahmad J et al, (13) who found thirty-eight young normoglycemic, non-obese, first degree relatives of type 2 diabetic subjects (FH+) and 38 control subjects without family history of diabetes (FH−) (age and sex matched),. First degree relative group (FH+) has higher C IMT ($p < 0.05$), BMI ($p < 0.05$).

Our results showed that females had high plasma leptin than males in type 2 DM, prediabetic and control groups.

Our study showed that in all participants, there was significant linear correlations between plasma leptin and the all-other factors except the creatinine (P-value <0.05). There were significant linear positive correlations between CIMT and all other factors (P-value <0.05).

We found at a cut off (15 ng/ml) of plasma leptin, the presence of increased carotid intima media thickness can be predicted with (81.5%) sensitivity and (66%) specificity(P-value0.028). These findings indicate that leptin plays an important role in promoting local stiffness of the carotid artery in patients with type 2 DM & prediabetes.

LIMITATIONS

Some of the limitations of this study include; this was a cross-sectional study therefore, we could not establish a causal relationship between leptin and carotid arterial stiffness, a single rather than multiple measurements of serum leptin which are known to follow a circadian pattern as well as the lack of detailed measurements of body fat and its distribution, insulin resistance, and plasma insulin levels. Antidiabetic treatment may also influence leptin levels, for example, glibenclamide sulfonylurea or insulin therapy, all increase serum leptin concentrations.

CONCLUSION

In conclusion, the present study shows that CIMT is significantly associated with leptin, independently of other cardiovascular risk factors well known to increase the thickness of the arterial wall. These results indicate that accelerating the development of atherosclerosis in diabetic patients type 2 more than 10 years and prediabetic patients but not in 1st degree relatives to diabetic patients. CIMT measurement is an effective, noninvasive tool which can assist in identifying people with diabetes and prediabetic who are at higher risk of developing microvascular and macrovascular complications. It may also help to evaluate the effectiveness of various treatment strategies used to treat people with diabetes. At a cut off (15ng/mL) of plasma leptin, the presence of increased carotid intima media thickness can be predicted with (81.5%) sensitivity and (66%) specificity (P-value 0.028. Since the prediabetic patients are at risk of developing atherosclerosis, they should be closely monitored.

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