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The correlation between serum leptin levels and lipid profile among non-obese type 2 diabetes mellitus patients and non-diabetic individuals

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Abstract

Background: Type 2 DM is a heterogeneous group of disorders characterized by insulin resistance, impaired insulin secretion, increased glucose production, and abnormal fat metabolism. Diabetes mortality primarily results from microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy, as well as macrovascular complications like coronary artery, peripheral vascular, and cerebrovascular diseases. Patients with diabetes usually have changes in adipose tissue metabolism and abnormalities in the secretion of adipokines such as leptin. The present study aims to study the relationship between serum leptin levels and lipid profile parameters among non-obese type 2 diabetes mellitus patients and non-diabetic individuals.

Methods: This hospital-based cross-sectional study was conducted among 41 type 2 diabetic patients and 41 non-diabetic individuals of both sexes between the ages of 40 and 70. Fasting blood glucose (FBS), serum leptin, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) levels were assayed.

Results: The mean serum leptin levels among diabetic patients were lower than those of non-diabetic individuals, and this difference in mean was statistically significant. The study showed a significant negative correlation between serum leptin, TC, TG, and low-density lipoprotein (LDL), and a positive correlation with HDL. In the final regression model, serum leptin showed a statistically significant association with FBS and HDL.

Conclusion: This study demonstrated that serum leptin levels can be a strong predictor of low HDL levels in diabetic patients. It can also contribute to raised levels of total cholesterol, triglyceride, and LDL, which are responsible for macrovascular complications in diabetics.

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Introduction

Diabetes mellitus, characterized by hyperglycemia, is a leading cause of death in developing countries. It is associated with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both (1). There is also increased hepatic glucose production, increased glucagon secretion, and abnormalities in adipocyte and lipid metabolism (2). The major defect in diabetes mellitus is the loss of glucose-induced insulin release, which results in relative insulin deficiency in the early stages of the disease and absolute insulin deficiency in the later stages (3). Increased free fatty acids in serum have also been implicated in beta cell failure. It can be due to lipotoxicity induced by apoptosis of islet cells (4). As a result of insulin resistance in adipose tissue, lipolysis occurs, and free fatty acid flux from adipocytes is increased. This leads to increased lipid synthesis, especially VLDL and triglyceride in hepatocytes. This is also responsible for the dyslipidemia found in type 2 DM (elevated triglycerides, reduced high-density lipoprotein (HDL), and increased low-density lipoprotein (LDL) particles) (5). Visceral and subcutaneous adipose tissue secrete a group of bioactive substances called adipocytokines. Adipocytokines like leptin are involved in the regulation of glucose and lipid metabolism (6). Leptin stimulates glucose uptake, increases the rate of glycolysis, and inhibits the activity of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) and glycogenolysis (7). All these mechanisms help to lower glucose levels. Leptin can stimulate adipocyte lipolysis by influencing hormone-sensitive Lipase (HSL) activity (8). Any defect in cholesterol ester homeostasis due to leptin or insulin deficiency can contribute to the increased incidence of atherosclerosis associated with type 2 diabetes (9). Leptin inhibits fatty acid synthase in the adipocytes, contributing to an overall fat mass reduction. Leptin induces the production of lipoprotein lipase and significantly decreases plasma TG (10). Leptin blocks the overaccumulation of TG in nonadipocytes, thereby confining fat storage to fat cells. Thus, leptin maintains a normal TG content and protects from fat overload and lipotoxicity. Leptin deficiency results in excess fat deposition and damage to nonadipocytes. Thus, the present study aimed to find the relationship between serum leptin levels and lipid profile parameters among type 2 diabetes mellitus patients and non-diabetic individuals.

Methods

This hospital-based cross-sectional study was conducted among people who visited the centralized clinical biochemistry laboratory under the Department of Biochemistry, Medical College Hospital, Thiruvananthapuram, during the period from February 2013 to January 2014. Simple random sampling from 41 type 2 diabetic patients (clinically diagnosed & FBS>126 mg/dl) and 41 non-diabetic individuals between 40 and 70 years of age of both sexes were selected. A total of 41 diabetic patients and 41 non-diabetic individuals were included according to the formula for 95% confidence limits and 80% power

$$N = 2 \times (Z\alpha \pm Z\beta)^2 \delta^2$$
$$(\mu 1 - \mu 2)^2$$
$$(Z\alpha \pm Z\beta)^2 = 7.849$$
$$\delta = 3.4 \text{ [standard deviation of leptin levels in the population (11)]}$$
$$(\mu 1 - \mu 2) = 2.1 \text{ (expected difference in mean)}$$

Patients with liver disease, renal disease, heart failure, stroke, obesity (BMI > 25 kg/m^2), pregnancy and lactation were excluded. The study was conducted after approval of the ethical committee (IEC No: 02/7/2012MCT). After obtaining informed written consent, the proforma was filled out, which contained the demographic data, past medical history, history of diabetes mellitus, history of addictions, sedentary lifestyles, and drug history. The height, weight, and BMI of study participants were noted. The weighing machine used was corrected to 0.5 kg. Before each measurement the machine was checked to zero error. Height was measured using a standard measuring scale. Body mass index was calculated by the formula:

$$\text{BMI} = \text{Weight in kg/ Height in m}^2$$

Only individuals with a BMI of < 25 Kg/m^2 were included in both study groups. After 12 hours of fasting and under strict aseptic precautions, 5 mL of blood was drawn from the cubital vein using disposable syringes and needles and collected in a non-vacuum clot activator tube. Blood for FBS estimation was collected in tubes containing sodium fluoride. The serum was separated by centrifugation at 3000 r.p.m for 10 minutes. Serum for FBS was immediately analyzed, and that for serum leptin and fasting lipid profile (FLP) was kept at -20^{0}C until analysis was carried out.

Estimation of fasting blood glucose and lipid profile was done in a fully automated analyzer (EM360) from Transasia Biomed, India. Blood glucose was assayed by the glucose oxidase method. Serum total cholesterol was determined by end point enzymatic method using cholesterol esterase and peroxidase. HDL was solubilized by a special reagent without disrupting other lipoproteins like LDL, VLDL, and chylomicrons. HDL cholesterol was enzymatically measured after the selective disruption. Serum triglyceride was assayed by the endpoint method (GPO Trinder method). Low-density lipoprotein was estimated using Friedwald's equation.

$$\text{LDL Cholesterol} = \text{Total cholesterol} - (\text{HDL} + \text{TG}/5)$$

Serum Leptin assay was done using an ELISA kit from Labor Diagnostika Nord GmbH & Co.KG, Am Eichenhain 1, 48531 Nordhorn on EL$_x$ 800MS,

ERBA MICROSCAN ELISA machine. The principle of the enzyme immunoassay test follows a typical two-step capture or sandwich-type assay. Statistical analysis was performed using SPSS for Windows version 16. The mean and standard deviation for quantitative variables were calculated for 41 diabetic and 41 non-diabetic individuals. Differences in means of quantitative variables between the two groups were compared by student t-test. The Pearson correlation coefficient was obtained to study the correlation between serum leptin and fasting blood glucose. A p-value of less than 0.05 was considered significant. Multivariate analysis was done using multiple linear regression analysis to study the difference in serum leptin levels among diabetic and non-diabetic individuals.

Results

The mean serum leptin level was 2.7ng/ml in diabetic patients and 7.9 ng/ml among the non-diabetic individuals. This difference in the mean of leptin levels was found to be statistically significant (p-value < 0.05) (Table 1). A statistically significant difference in the mean of serum leptin levels was observed in males and females among both diabetic patients and non-diabetic individuals. Among the diabetic males, the mean of leptin levels was 2.1 + 0.8; among diabetic females, it was 3.3 + 0.7. The mean leptin levels among non-diabetic males and females were 5.6 + 2.1ng/ml and 10.8 + 1.8ng/ml respectively (Table 2). This showed that females have higher serum leptin levels than males in both groups. The mean total cholesterol values in diabetic patients and non-diabetic individuals were 248.2 + 59.2 and 179 + 39.5 mg/dl, respectively. The mean triglyceride levels were 152.1 + 40.1 and 98.5 + 29.2 mg/dl among the two groups. The mean serum LDL levels of diabetic patients and non-diabetic individuals were 181.2 + 52.6 and 121.4 + 36 mg/dl, and the mean HDL was 33.3 + 9.2 and 37.9 + 6.1, respectively (Table 1). Thus, the present study showed that in diabetic patients, there was elevated serum total cholesterol, triglyceride & LDL, and decreased HDL levels compared to nondiabetic individuals. Our study also showed a significant negative correlation between serum leptin and total cholesterol, triglyceride, and LDL, while a positive correlation with HDL. In multivariate analysis, total cholesterol, triglyceride, and LDL did not show a significant relation (p-value > 0.05) with serum leptin in the first regression model and was eliminated. In the final regression model obtained by step-wise procedure, serum leptin showed a statistically significant association with FBS and HDL. The two parameters, FBS and HDL, can predict a 47.7% variation in serum leptin (Tables 3 and 4). The equation for predicting serum leptin levels shows that a one unit increase in leptin is produced by 0.079 times increase in HDL and 0.016 times decrease in FBS.

Table 1. Various study parameters among diabetic patients and non-diabetic individuals

Variables		Mean	Standard deviation	Median	Minimum	Maximum	t	p
FBS	Diabetic	335.5	85.7	308	222	538	4.400	< 0.001
	Non diabetic	81.7	6.9	82	60	90		
Leptin	Diabetic	2.7	0.9	2.6	1.4	4.8	- 9.934	< 0.001
	Non diabetic	7.9	3.2	8.7	2	11.0		
Total cholesterol	Diabetic	248.2	59.2	258	132	406	6.223	< 0.001
	Non diabetic	179	39.5	181	105	279		
Triglyceride	Diabetic	152.1	40.1	152	71	261	6.917	< 0.001
	Non diabetic	98.5	29.2	90	60	64		
HDL	Diabetic	33.3	9.2	33	13	52	- 2.608	< 0.011
	Non diabetic	37.9	6.1	37	29	320		
LDL	Diabetic	181.2	52.6	187	82	212	6.003	< 0.001
	Non diabetic	121.4	36	119	48	64		

(FBS- Fasting blood sugar, HDL- high-density lipoprotein, LDL- low-density lipoprotein)

Table 2. Comparison of mean of serum Leptin levels in both genders

LEPTIN		N	Mean	Std	t	p
Male	Diabetic	22	2.1	0.8	- 7.366	< 0.001
	Non diabetic	23	5.6	2.1		
Female	Diabetic	19	3.3	0.7	- 16.765	< 0.001
	Non diabetic	18	10.8	1.8		

Table 3. Correlation of serum leptin levels with total cholesterol, triglyceride, HDL, LDL.

Subject / Correlation	Leptin / Total cholesterol	Leptin / Triglyceride	Leptin / HDL	Leptin / LDL
Pearson correlation (r)	- 0.381	- 0.482	0.332	- 0.376
P-value	< 0.001	< 0.001	0.002	0.001
N	82	82	82	82

Table 4. Multivariate analysis using multiple linear regression between serum leptin levels, FBS, HDL

Subject	Unstandardized coefficient		Standardized coefficient	t	p
	B	Std error	Beta		
Constant	5.769	1.475		3.912	< 0.001
FBS	- 0.016	0.002	- 0.635	-7.671	< 0.001
HDL	0.079	0.036	0.181	2.189	0.032

Discussion

The results obtained from our study showed that the mean of serum leptin levels among diabetic patients was 2.7 + 0.9, and in non-diabetic individuals was 7.9 + 3.2. Moriya et al. also found poorly controlled Type 2 DM can reduce serum leptin levels (12). On the other hand, Tuominen et al. found fasting plasma leptin levels were higher in DM than in controls (13). Haffner et al. reported that leptin concentrations were not different in diabetic and non-diabetic subjects (14). Thus, the different observations made by various researchers evoked the need for the present study. Our study observed low serum leptin levels in diabetic patients compared to non-diabetic individuals. Although mean serum leptin levels are lower among diabetics, females have higher levels than males. Diabetic patients also have elevated TC, TG, LDL, and low HDL levels. A study by Zoe S.K Lee and Juliana C.N et al. stated that diabetic patients had high serum total cholesterol, triglyceride, LDL, and low HDL, similar to our study results (15). The strong negative correlation observed in this study between serum leptin and TC, TG & LDL is highly suggestive of the role of leptin in the production of hyperlipidemia in type 2 DM patients. However, a positive correlation between leptin and HDL can explain the low HDL levels in DM. Hiroshi Hirose, Ikuo Saito, et al. observed a negative correlation between leptin and total cholesterol, triglyceride & LDL, similar to our study result (16). Therefore, this study clearly established the relation of low serum leptin with elevated TC, TG & LDL, and low HDL, responsible for life-threatening complications such as atherosclerosis, thromboembolism, MI, and CVA.

Conclusion

It can be concluded that the low serum leptin levels observed among the diabetic patients in the present study can lead to high total cholesterol, triglyceride, LDL, and low HDL levels.

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No funding was obtained from any organizations for the study to be conducted.

Ethical statement

Institutional Ethical Committee (IEC No: 02/7/2012MCT)

Conflicts of interest

The authors declare that there is no conflict of interest.

Author contributions

Chandralekshmy Chandrika is the study's principal investigator and major contributor in writing the manuscript; Archana Jayan helped with statistical analysis; Fathima Beevi Osman gave complete guidance and review of the study results.

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