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RESEARCH ARTICLE OPEN ACCESS

Serum leptin as an indicator of dyslipidaemia in non-obese type 2 diabetic patients: A cross-sectional study in Jordan

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Abstract
Objective: This study evaluated how serum leptin levels are associated with lipid profiles in non-obese adults with T2DM in comparison to age- and sex-matched non-diabetic controls in Jordan.
Methods: In this hospital-based cross-sectional study, we analysed laboratory records from March to December 2024 for 60 non-obese (BMI <25 kg/m²) adults with T2DM and 60 non-diabetic controls, for age (40-70 years) and sex (30 males and 30 females per group). Data included BMI, FBS, serum leptin, TC, TG, LDL-C, and HDL-C. Between-group comparisons used independent t-tests. The study examined associations via Pearson's correlation along with a multiple linear regression analysis.
Results: The T2DM mean group was significantly higher FBS (340.29 ± 34.00 vs. 77.67 ± 4.27 mg/dL, p<0.001), TC, TG, and LDL-C, and lower HDL-C and serum leptin (2.83 ± 0.55 vs. 7.77 ± 1.65 ng/mL, p<0.001). Leptin correlated negatively with TC (r=-0.635), TG (r=-0.540), and LDL-C (r=-0.514), and positively with HDL-C (r=0.669) (all p<0.001). In regression analysis, independent predictors of leptin levels were FBS (β = -0.015, p<0.001) and HDL-C (β = 0.269, p<0.001).
Conclusion: Non-obese adults had lower serum leptin levels in T2DM Subjects and showed significant inverse associations with atherogenic lipids and a positive association with HDL-C. So, leptin may be a useful biomarker of dyslipidaemia in non-obese T2DM, warranting further prospective investigation

Keywords: Leptin, Dyslipidaemia, Type 2 Diabetes Mellitus, Non-obese, Jordan

Plain English Summary

This study looked at leptin, a hormone in the blood, in Jordanian adults who have type 2 diabetes but are not obese, and compared them to people without diabetes. We found that the diabetic patients had unhealthier cholesterol and fat levels, along with lower leptin. Lower levels of the hormone leptin were strongly linked to a poorer cholesterol profile. This implies that measuring the levels of the hormone could help doctors understand the risks of heart problems in diabetic people, even if the patients are not overweight.

Introduction

DM continues to be a major health concern worldwide, with Jordan being no exception in hosting a high burden of the disease. Among Jordanian adults, 21.1% suffer from the disease, the majority of which being cases of T2DM (1, 2). Though obesity is a primary cause of T2DM, a considerable percentage of T2DM patients are not obese. This phenomenon of non-obese T2DM is common among specific ethnic groups and requires specific attention (3).

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Dyslipidaemia, with high triglycerides, low HDL-C, and high LDL-C, frequently accompanies T2DM and significantly contributes to the disease (4). Insulin resistance, the primary cause of T2DM, further adds to the complexity of lipid metabolism, thus posing a threat (5).

Leptin, a hormone from adipocytes, is important regulating energy and carbohydrate homeostasis as well as lipid metabolism. It stimulates fatty acid oxidation and inhibits fat synthesis (6). In obese people, however, the hormone tends to become resistant, thus leading to a series of metabolic complications (7). In the case of non-obese people, the exact role of the hormone in the context of diabetic dyslipidaemia still remains a mystery. Some studies show hormone levels in T2DM patients being lower than in healthy controls, while others show the opposite (8, 9).

In Jordan, the relationship of the hormone with metabolic markers in T2DM patients who are not obese has not been investigated in the recent past. Therefore, the current work compares the hormones in non-obese T2DM patients with those of healthy controls in the country. This could pave the way for the hormone to act as a potential marker for dyslipidaemia.

Materials and Methods

This is a cross-sectional study in a major private medical laboratory in Jordan, which caters to a broad population of out- and inpatients. The research team accessed anonymised data from the medical laboratory for a specific period between March and December 2024. This provided a contemporary dataset that reflected the latest trends in the population under consideration. This medical laboratory caters to a broad population of out- and inpatients, which reflects the larger population of non-obese individuals, and thus the results can be generalised for the same population of non-obese individuals.

Participants

The study sampled 120 adults, aged 40-70 years, into two groups: 60 individuals with a clinical diagnosis of T2DM and 60 non-diabetic controls. 30 men and 30 women were included in both the T2DM and non-diabetic control groups to control for the confounding variable of sex. They were non-obese group if they had a BMI of less than 25 kg/m², as recommended for the definition of the normal weight group (10).

Inclusion Criteria

We included adults (40–70 years) with a BMI <25 kg/m², ensuring our entire sample was non-obese. This allowed us to focus on metabolic differences independent of obesity-related factors.

Exclusion Criteria

We excluded individuals with histories of liver, kidney, cardiac, or endocrine disorders, as these could independently alter metabolic parameters. Other exclusions were pregnancy or lactation, acute/chronic infections, inflammatory diseases, and recent initiation (within three months before sampling) of lipid-lowering therapy. T2DM diagnosis followed American Diabetes Association guidelines: either a prior clinical diagnosis or meeting biochemical criteria (HbA1c ≥ 6.5% or fasting blood glucose ≥ 126 mg/dL in two different times) (11).

Data Collection and Laboratory

We collected anthropometric and demographic information: age, sex, weight, and height. BMI was measured in kilograms, which is divided by height (in meters squared). We took fasting blood samples following a 10–12-hour overnight fast. FBS was calculated by a glucose oxidase/peroxidase method on an Accu-Check Aviva analyser (Germany). Serum TC, TG, and HDL-C were quantified via enzymatic colourimetric assays on a Humastar 80 Auto Analyser (Human, Germany). LDL-C was measured by the Friedewald formula, and serum leptin with a commercial ELISA kit (BioVendor, Czech Republic, Cat. # RD191001100). The assay's sensitivity appeared as X ng/mL, with intra- (variation of X%) and inter-assay coefficients (of Y%).

Statistical Analysis

The current article employed IBM SPSS Statistics, Version 23.0. Continuous variable normality was checked by the Shapiro-Wilk test. Then, normally distributed data is mean ± SD. The comparison of the group utilised independent samples t-tests. We examined the linear association between leptin and metabolic markers using Pearson's correlation and multiple linear regression with serum leptin as the dependent variable and FBS and HDL-C as independent predictors, adjusting for age, sex, and BMI. We assessed multicollinearity using VIF. Statistical significance was set at $p < 0.05$.

Results

Baselines

120 participants were equally split into a T2DM group and a non-diabetic control group, each with 30 men and 30 women. Mean ages were similar between groups. By design, all participants were non-obese (BMI <25 kg/m²), with no significant differences in BMI between groups (Table 1).

Table 1: Comparing Clinical and Metabolic Parameters between T2DM and Non-Diabetic Groups

Parameter (Unit)	T2DM Group (n=60)	Non-Diabetic Group (n=60)	t-statistic	p-value
Age (years)	XX.X ± X.X	XX.X ± X.X	X.XXX	X.XXX
BMI (kg/m²)	XX.X ± X.X	XX.X ± X.X	X.XXX	X.XXX
FBS (mg/dL)	340.29 ± 34.00	77.67 ± 4.27	59.361	<0.001
Leptin (ng/mL)	2.83 ± 0.55	7.77 ± 1.65	-21.951	<0.001
Total Cholesterol (mg/dL)	263.10 ± 28.95	177.59 ± 16.73	19.812	<0.001
Triglycerides (mg/dL)	154.17 ± 19.32	99.56 ± 18.84	15.675	<0.001
HDL-C (mg/dL)	34.15 ± 5.04	38.29 ± 3.10	-5.42	0.002
LDL-C (mg/dL)	185.88 ± 25.18	126.05 ± 19.54	14.542	<0.001

Comparative Analysis of Metabolic Parameters

As expected, the T2DM group had markedly higher FBS levels (340.29 ± 34.00 mg/dL) compared to controls (77.67 ± 4.27 mg/dL, p<0.001). Their lipid profile was also significantly more atherogenic, with higher TC, TG, and LDL-C, and lower HDL-C (all p<0.05). Notably, serum leptin levels were significantly lower in the T2DM group (2.83 ± 0.55 ng/mL) than in controls (7.77 ± 1.65 ng/mL, p<0.001). This pattern held for both men and women (Table 2).

Table 2: Serum Leptin Levels Stratified by Sex

Sex	Group	n	Leptin (ng/mL), Mean ± SD	p-value
Male	T2DM	30	2.68 ± 0.60	<0.001
	Non-Diabetic	30	7.39 ± 1.92	
Female	T2DM	30	2.98 ± 0.45	0.007
	Non-Diabetic	30	8.16 ± 1.26	

Correlation and Regression Analyses

We found strong correlations between serum leptin and lipid measures. Leptin was in a negative correlation with TC (r = -0.635), TG (r = -0.540), and LDL-C (r = -0.514), and positive with HDL-C (r = 0.669) (all p<0.001; Table 3).

Table 3: Pearson's Correlations between Serum Leptin and Lipid Parameters (N=120)

Lipid Parameter	Correlation Coefficient (r)	p-value
Total Cholesterol	-0.635	<0.001
Triglycerides	-0.54	<0.001
HDL-C	0.669	<0.001
LDL-C	-0.514	<0.001

In multiple linear regression, FBS and HDL-C emerged as independent predictors of leptin levels. Each 1 mg/dL increase in FBS was linked with a 0.015 unit drop in leptin (B = -0.015, 95% CI: -0.018 to -0.012, p<0.001). Conversely, each 1 mg/dL increase in HDL-C was linked to a 0.269 unit increase in leptin (B = 0.269, 95% CI: 0.235 to 0.303, p<0.001). The model explained approximately X% of the variance in leptin levels (Adjusted R^2 = 0.47; Table 4).

Table 4: Multiple Linear Regression of Serum Leptin Level Predictors

Predictor	Unstandardized Coefficient (B)	95% CI for B	Standardised Coefficient (Beta)	t-value	p-value
Constant	-1.346	(-2.689, -0.003)	-	-1.978	0.05
FBS	-0.015	(-0.018, -0.012)	-0.714	-24.511	<0.001
HDL-C	0.269	(0.235, 0.303)	0.452	15.511	<0.001

Dependent Variable: Serum Leptin (ng/mL). Adjusted R^2 = 0.47.

Discussion

Our investigation demonstrates that interestingly, circulating leptin levels are significantly decreased in non-obese Jordanian individuals suffering from T2DM compared to their non-diabetic counterparts, along with the expected changes in lipid profile, favouring atherosclerosis. We found that circulating leptin levels decrease as TC, TG, and LDL-C levels increase, and vice versa for HDL-C levels. Most importantly, FBS and HDL-C levels emerged as predictors of circulating leptin levels.

The decreased levels of circulating leptin in non-obese T2DM individuals are consistent with

some previous studies, though other studies have shown contradictory results (12, 13). In most of the studies with higher levels of circulating leptin in individuals suffering from diabetes, the subjects studied were obese (9). This shows that adiposity is a significant in regulating leptin levels.

In the case of non-obese individuals suffering from T2DM, several factors may contribute to decreased levels of circulating leptin, including altered adipokine secretion from visceral adipose tissue, chronic inflammation, and metabolic stress of hyperglycaemia and insulin resistance, leading to decreased production of leptin and/or increased clearance of leptin from the circulation (14). We observed that FBS levels are inversely proportional to circulating leptin levels, showing that hyperglycaemia is important in decreased leptin levels.

The significant correlations between leptin and lipid components are also very compelling. It is well documented that leptin has the capacity to enhance fatty acid oxidation and inhibit lipogenesis in peripheral tissues (7). It is possible that lower levels of leptin, as seen in our diabetic population, may compromise the effectiveness of such anti-lipidaemic mechanisms, thereby contributing to the dyslipidaemia seen in our population, with higher levels of TG and LDL-C, and decreased levels of HDL-C. These findings are consistent with those of Akinjinmi et al., who also reported similar inverse correlations between leptin and atherogenic lipids in diabetes (15). Moreover, the positive correlation between leptin and HDL-C may indicate leptin involvement in the promotion of reverse cholesterol transport, an important mechanism in the protection against heart disease.

We also verified the well-known phenomenon of sexual dimorphism in the levels of leptin, where women have higher levels than men, probably because of more subcutaneous fat stores and hormonal influences (16). However, diabetes has a very strong depressing effect on leptin levels in both sexes, again confirming the widespread influence of metabolic disorders on adipokine signalling pathways.

Strengths and Limitations

Our study design has some advantages. We matched the groups for age and gender, making the study more robust. By studying the non-obese T2DM phenotype, we filled the gap in the study of this group, who are usually not considered in studies on obesity-related metabolic problems. We used standardised laboratory procedures, making the study more reliable.

Some limitations must be highlighted. First, a cross-sectional study cannot establish causality between variables. We can only show associations between the variables. Secondly, the calculation of LDL-C using the Friedewald formula may not be accurate, especially if triglyceride levels are high, making the interpretation of the lipid profile difficult. We did not have information on the duration of diabetes, medications, diet, physical activity, and body composition, making the study more difficult to interpret. Although the sample size is adequate for the study, the study is from a single centre, making it difficult to generalise to other groups except the Jordanian Arabs.

Conclusion

In conclusion, it has been noted that non-obese T2DM patients have lower levels of leptin, and such lower levels of leptin show a significant correlation with an unfavourable lipid profile. This indicates the leptin importance as a potential marker for the identification of dyslipidaemia in non-obese T2DM patients, thus suggesting the metabolic links between T2DM and lipid profiles, which are independent of body weight. To understand the role of leptin in a more precise manner, it is important to conduct more studies, including insulin sensitivity, visceral adiposity, and the use of medications.

List of Abbreviations

ADA: American Diabetes Association
BMI: Body Mass Index
CVD: Cardiovascular Disease
ELISA: Enzyme-Linked Immunosorbent Assay
FBS: Fasting Blood Sugar
HDL-C: High-Density Lipoprotein Cholesterol
LDL-C: Low-Density Lipoprotein Cholesterol
SD: Standard Deviation
T2DM: Type 2 Diabetes Mellitus
TC: Total Cholesterol
TG: Triglycerides

Declarations

Ethics Approval and Consent to Participate

The individual informed consent requirement was waived by the ethics committee based on the ethics of the Declaration of Helsinki.

Consent for publication

All authors gave consent for publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Data Availability

The anonymised datasets generated can be found from the corresponding author upon when needed

Competing Interests

There are no competing interests.

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Author Contributions
AAM: Data Curation, Investigation, Software, Formal Analysis.
ARMA: Investigation, Resources, Project Administration.
CK: Supervision, Funding Acquisition, Writing - Review & Editing, Project Administration.
KAM: Methodology, Validation, Resources, Writing - Review & Editing, Supervision.
MWT: Conceptualisation, Investigation, Formal Analysis, Writing - Original Draft, Visualisation.
SL: Validation, Writing - Review & Editing, Visualisation.

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