

# Association of Serum Leptin and Adiponectin Concentrations with Type 2 Diabetes Biomarkers and Complications Among Saudi Women

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**Objective:** Hyperglycemia and insulin resistance (IR) put obese women with Type 2 diabetes mellitus (T2DM) at risk for cardiovascular disease (CVD).

**Methods:** 150 T2DM women aged 30–45 were studied cross-sectionally at Madinah Hospital lab to find T2DM risk factors and their association with adiponectin/leptin levels.

**Results:** Women with T2DM showed greater fasting blood glucose (FBG), hemoglobin A1c (HbA1c), triglycerides (TG), body mass index (BMI), waist circumference (WC), insulin resistance (IR), high-sensitivity C-reactive protein (hs-CRP), and CVD risk (high atherogenic index of plasma (AIP) and leptin), but decreased high-density lipoprotein (HDL-cholesterol) and poor insulin sensitivity with low adiponectin. Obese women with T2DM had increased leptin and reduced adiponectin. Leptin levels were significantly related to IR, BMI, and AIP ( $B = 3.97$ ,  $P = 0.02$ ) but not WC. Leptin levels were negatively correlated with insulin sensitivity (IS) and HDL-c ( $P < 0.05$ ). In linear regression analysis, adiponectin levels had a significant association with IS and HDL-c ( $P = 0.03$ ,  $P = 0.04$ ) but an inverse relationship with IR, BMI, WC ( $B = -2.91$ ,  $P = 0.04$ ), and AIP ( $P < 0.05$ ).

**Conclusion:** Increased leptin levels are related to high IR, AIP, and BMI among T2DM female patients. Similarly, adiponectin levels decrease IS and HDL-c. Therefore, obese T2DM women with high leptin and low adiponectin levels should be periodically checked to avoid or decrease consequences like CVD.

**Keywords:** adiponectin, cardiovascular disease, insulin resistance, leptin, obesity, type 2 diabetes

## Introduction

Type 2 diabetes mellitus (T2DM) accounts for 90% of all diabetes cases and can be characterized by hyperglycemia, insulin resistance (IR), and insufficiency. It is reported that diabetes mellitus (DM) has a substantial economic impact; the indirect national financial burden is anticipated to be over 0.87 billion USD, and patients with diabetes have about ten times greater healthcare expenses than those without diabetes (3686\$ vs 380\$).<sup>1–3</sup> Diabetes affects 31.6% of Saudi Arabia's (KSA) population, among which 27.6% are women.<sup>4</sup> Reportedly, cardiovascular disease (CVD) is a prevalent consequence of DM, and it continues to be the major cause of mortality and disability among DM patients. According to a Saudi Scientific Diabetes Society research, > 50% of DM patients die from cardiovascular reasons. The number of DM patients with higher cardiovascular risk is predicted to provide a significant challenge to the healthcare systems of KSA, and the proportion of DM survivors of cardiovascular events is rising globally.<sup>5</sup> According to World Health Organization 2021 reports, 33.7% of Saudis are obese, and 68.2% are overweight, demonstrating that preventive measures are missing or inefficient.<sup>5,6</sup>

Obese people are at risk for diabetes, CVD, stroke, cancer, and obstructive sleep apnea. Better knowledge of DM, CVD, and obesity pathogenesis linkages is needed to create innovative techniques for lowering patient health problems and discovering new diagnostic biomarkers. Leptin is a 16-kDa protein hormone that regulates appetite and energy balance. Leptin has a key function in the pathogenesis of obesity and IR.<sup>7</sup> Experimental investigations show that serum

leptin regulates brain glucose. Some studies found a high connection between diabetes biomarkers and leptin levels,<sup>8</sup> while others found none.<sup>7</sup> Adiponectin, another adipokine, protects against IR/diabetes and atherosclerosis. Reduced adiponectin levels may contribute to T2DM, obesity, and CVD. Adiponectin regulates insulin sensitivity, glucose, lipid metabolism, and cardiovascular homeostasis.<sup>9</sup> Leptin and adiponectin are hormones secreted from adipose tissue; leptin promotes metabolism and lowers hunger, while adiponectin mediates insulin-sensitizing action. Abnormal levels of leptin are linked to obesity and IR. Greater adipose tissue (body fat) mass and IR raise leptin levels, whereas higher body fat mass and insulin sensitivity reduce adiponectin levels.

As Saudi females have a greater incidence of T2DM, obesity, and CVD, leptin and adiponectin levels with T2DM biomarkers and comorbidities were evaluated with the expectation that leptin, adiponectin, and T2DM consequences, including CVD, would be linked to obese status.

## Methodology

Cross-sectional research was done between 2021–2022 on 150 women with T2DM aged between 30–45. In contrast, T2DM was defined by hemoglobin A1c (HbA1c) 6.5% (48 mmol/mol), fasting blood glucose (FBG)  $\geq 126$  mg/dL, self-reported use of insulin or oral hypoglycemic medicines, or physician diagnosis.<sup>6</sup> The study at Madinah hospital laboratories identified biological and behavioral risk factors for T2DM and adiponectin/leptin as described.

## Biological Factors

- Anti-hypertriglyceridemic, anti-hyperlipidemic, and anti-hypertensive medication (each) usage was identified as “yes” for use or “no” for nonuse.
- Fasting insulin, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol (TC), triglyceride (TG), FBG, HbA1c, and high sensitive-C-reactive protein (hs-CRP), were measured from blood samples using standard laboratory techniques.
- In diabetic patient serum, leptin and adiponectin hormones were determined via quantitative Enzyme-Linked Immunosorbent Assay (ELISA) based chemiluminescent assay (CUSABIO Technology LLC, Houston, USA). The performed processes were constructed according to the manufacturer’s instructions, and the mean absorbances of the standards and samples were determined in triplicate. Leptin and adiponectin levels reference range according to the kit’s manufacturer are 0.5–15.5 ng/mL and 5–30  $\mu$ g/mL, respectively.
- Using fasting values, IR was measured using the homeostasis model assessment-estimated insulin resistance (HOMA-IR index) =  $[\text{glucose (mmol/L)} * \text{insulin (U/mL)}] / 22.5$ . The contributors were categorized according to the tertiles of HOMA-IR into low, middle, and high-level groups. The lower tertile was defined as HOMA-IR  $< 1.8$ ; the middle was HOMA-IR  $> 1.9$ , and the upper was HOMA-IR  $> 2.9$ .<sup>10</sup> Insulin sensitivity was measured using the Quantitative Insulin Sensitivity Check (QUICKI) Index, which is 0.45 in healthy people and 0.30 in people with diabetes<sup>11</sup> while IR is below 0.39.
- The AIP ( $\log_{10} \{ \text{TG/HDL-c} \}$ ) was calculated as an atherogenic dyslipidemia index. The AIP is categorized as low risk for CVD ( $< 0.1$ ), medium risk (0.1–0.24), and high risk ( $> 0.24$ ).<sup>12</sup>

## Behavioral Factor

- Smoking status was identified as previous, current, and never smokers.
- Physical activity was evaluated with a four-domain physical activity assessment instrument: (1) active living, (2) work, (3) home/garden, and (4) sport/exercise indexes. These scores vary from 1 to 5, with higher scores indicating a higher level of physical activity. The sum of these four domain scores was utilized to calculate a total score with a maximum value of 20.<sup>13</sup>
- Body mass index (BMI), weight, and height were determined twice using an electronic scale (Beurer GmbH Type PS 07, China). The contributors were categorized according to the tertiles of the BMI, such as underweight ( $< 18.5 \text{ Kg/m}^2$ ), normal ( $18.5\text{--}25.0 \text{ Kg/m}^2$ ), overweight ( $25.0\text{--}29.9 \text{ Kg/m}^2$ ), or obese ( $> 30.0 \text{ Kg/m}^2$ ).<sup>6</sup>
- Waist circumference (WC) was measured to the nearest centimeter at the belly button. Women with a WC  $\geq 88$  cm were considered abdominally obese, while women with WC  $< 88$  cm were considered abdominally non-obese.<sup>6</sup>

## Statistical Analysis

GraphPad Prism 7 was used for statistics (GraphPad Software, CA, USA). Continuous data were reported as mean SD (Mean  $\pm$  Standard deviation) and categorical data as numbers (%). One-way ANOVA was used to compare research categories. Pearson's correlation was used to compare leptin, adiponectin, glucose, HbA1c, insulin, hs-CRP, lipid profile, BMI, and AIP. Multiple linear regression was utilized to investigate serum leptin and adiponectin's impact on T2DM indicators, obesity markers, and CVD risk variables. Serum leptin and adiponectin levels were used as the independent variable, and several dependent variables. Multiple linear regression was run twice on serum leptin and serum adiponectin levels in diabetic women to generate unstandardized coefficients (B) with 95% confidence intervals. All differences were signified at  $P \leq 0.05$  or  $P \leq 0.001$ .

## Results

### General Characteristics of Participants with T2DM

Women with T2DM average age was 55.5 years, while 36.7%, 30%, and 46.7% were prescribed anti-hypertriglyceridemic, anti-hyperlipidemic, and anti-hypertensive medications, respectively, and were less physically active. These participants also had higher FBG, HbA1c, triglycerides, BMI, WC, HOMA-IR, hs-CRP and were at higher risk of CVD (high AIP) and high leptin levels but lower HDL-c and low insulin sensitivity with low adiponectin level (Table 1).

**Table 1** Characteristics of Women with T2DM

Parameters	Diabetic n= 150	Reference Range
Age (years) <sup>§</sup>	55.5 $\pm$ 10.5	–
Smoking habit <sup>#</sup>		
Previous	20(13.3%)	–
Current	10(6.7%)	–
Never	120 (80%)	–
Anti-hypertriglyceridemic medication <sup>#</sup>		
Yes	55(36.7%)	–
No	95(63.3%)	–
Anti-hyperlipidemic medication <sup>#</sup>		
Yes	45(30%)	–
No	105(70%)	–
Anti-hypertensive medication <sup>#</sup>		
Yes	70(46.7%)	–
No	80(53.3%)	–
Duration of diabetes (years) <sup>§</sup>	12.5 $\pm$ 5.2	–
FBG (mmol/L) <sup>§</sup>	<b>7.1<math>\pm</math>0.87</b>	3.89–5.50
HbA1c (%) <sup>§</sup>	<b>7.51<math>\pm</math>2.56</b>	4.3–6.0
LDL-c (mmol/L) <sup>§</sup>	2.97 $\pm$ 0.95	2.59–4.11
HDL-c (mmol/L) <sup>§</sup>	<b>1.03<math>\pm</math>0.40</b>	1.04–1.55
Total cholesterol (mmol/L) <sup>§</sup>	5.98 $\pm$ 0.84	5.2–6.2

(Continued)

**Table 1** (Continued).

Parameters	Diabetic n= 150	Reference Range
Triglycerides (TG) (mmol/L) <sup>§</sup>	<b>2.89±2.64</b>	1.7–2.2
BMI (kg/m <sup>2</sup> ) <sup>§</sup>	<b>29.77±8.86</b>	18.5–25.0
Waist circumference (WC) cm	<b>112±12.16</b>	< 88
Physical activity <sup>§</sup>	8.9±2.26 (Middle activity)	Total score with a maximum value of 20
Leptin ng/mL <sup>§</sup>	<b>25.7±10.12</b>	0.5–15.5
Adiponectin µg/mL <sup>§</sup>	<b>5±3.02</b>	5–30
hs-CRP(mg/l) <sup>§</sup>	<b>17.9±6.17</b>	<10
Fasting insulin (µU/mL) <sup>§</sup>	7.9±5.55	< 25
Insulin Resistance (IR) <sup>§</sup>	<b>2.5±1.71</b>	< 1.8
Insulin Sensitivity (IS) <sup>§</sup>	<b>0.4±0.11</b>	>0.45
AIP <sup>#,§</sup>		
Low Risk	20(13.3%), 0.08±0.02	< 0.1
Middle Risk	60(40%), 0.15±0.08	0.1–0.24
High Risk	<b>70(46.7%), 0.25±0.12</b>	>0.24

**Notes:** <sup>#</sup>Numbers (%) and <sup>§</sup>Values were Mean ± standard deviation were shown. Bold values were considered abnormal values. References range obtained from Madinah Hospital labs at Madinah region, Saudi Arabia.

## Participants' Characteristics According to HOMA-IR Index and BMI Categories

Table 2 shows the participants' biological and anthropometric data. Participants were separated into three groups according to the HOMA-IR tertile range, ie, lower tertile HOMA-IR <1.8 (20(13.3%)), HOMA-IR index ≥1.9 (60(40%)) is middle tertile. Upper tertile: HOMA-IR ≥2.9 (70(46.7%)). Clinical and anthropometric data were evaluated using a one-way ANOVA. FBG, HDL-c, TG, BMI, WC, hs-CRP, leptin, adiponectin, and IS differed amongst the HOMA-IR groups. High HOMA-IR T2DM

**Table 2** Characteristics of Participants According to the Insulin Resistance (HOMA-IR) Index

Parameters	Low Tertile < 1.8	Middle Tertile> 1.9	Upper Tertile > 2.9	P-value
n= No. of samples	n=20(13.3%)	n=60(40%)	n=70(46.7%)	-
FBG (mmol/L)	6.44±0.27	6.92±0.77	7.90±0.83	0.04*
HbA1c (%)	6.55±2.66	6.61±2.62	6.85±3.26	>0.05
LDL-c (mmol/L)	2.79±0.85	2.85±0.73	3.01±0.97	>0.05
HDL-c (mmol/L)	1.04±0.45	1.0±0.20	0.99±0.50	0.03*
Total cholesterol (mmol/L)	4.78±0.83	4.98±0.86	5.88±0.89	>0.05
Triglycerides (TG) (mmol/L)	2.45±1.64	2.79±2.54	3.39±2.61	0.03*

(Continued)

**Table 2** (Continued).

Parameters	Low Tertile < 1.8	Middle Tertile > 1.9	Upper Tertile > 2.9	P-value
BMI (kg/m <sup>2</sup> )	25.17±9.86	28.77±10.56	29.67±7.86	0.04*
Waist circumference (WC) cm	112±10.16	115±12.10	120±10.11	0.03*
Leptin ng/mL	20.7±11.12	23.9±9.12	26.7±11.9	0.02*
Adiponectin µg/mL	5±2.03	4.5±1.12	4.2±1.01	0.03*
hs-CRP(mg/l)	18.9±6.17	22.9±10.11	25.6±9.13	0.04*
Fasting insulin (mIU/L)	6.3±2.51	6.8±2.61	8.5±3.54	0.02*
Insulin Sensitivity (IS)	0.28±0.11	0.15±0.09	0.12±0.08	0.02*
AIP <sup>#</sup>				
Low Risk	5(25%)	13(21.7%)	2(2.9%)	>0.05
Middle Risk	11(55%)	20(33.3%)	29(41.4%)	>0.05
High Risk	4(20%)	27(45%)	39(55.7%)	0.05*

**Notes:** Data were expressed as the mean ± (SD) for continuous variables, P-value obtained from one-way ANOVA. \*P≤0.05. <sup>#</sup>AIP data were presented as numbers (%).

women had increased leptin and reduced adiponectin. High HOMA-IR candidates had high BMI and WC. The high HOMA-IR group with high CVD risk, evaluated by AIP, had higher TG and hs-CRP values but lower HDL-c and IS.

**Table 3** summarizes the characteristics of 150 diabetic people according to BMI tertiles such as 15.3% is normal (18.5–25.0Kg/m<sup>2</sup>), 41.3% is overweight (25.0–29.9Kg/m<sup>2</sup>), and 43.4% is obese (>30.0Kg/m<sup>2</sup>). However, the BMI of the three groups differed significantly. FBG differed between normal (6.41), overweight (6.90), and obese (7.93), and

**Table 3** Characteristics of Participants According to BMI Categories

Parameters	Normal (18.5–25.0Kg/m <sup>2</sup> )	Overweight (25.0–29.9Kg/m <sup>2</sup> )	Obese (>30.0Kg/m <sup>2</sup> )	P-value
n= No. of samples	n=23(15.3%)	n=62(41.3%)	n=65(43.4%)	–
FBG (mmol/L)	6.41±0.37	6.90±0.87	7.93±0.93	0.04*
HbA1c (%)	6.45±2.61	6.71±2.72	6.95±3.36	>0.05
LDL-c (mmol/L)	2.59±0.75	2.75±0.72	3.21±0.96	>0.05
HDL-c (mmol/L)	1.05±0.47	1.1±0.23	0.90±0.55	0.03*
Total cholesterol (mmol/L)	4.88±0.82	4.95±0.87	5.89±0.79	>0.05
Triglycerides (TG) (mmol/L)	2.55±1.61	2.89±2.51	3.79±2.31	0.03*
Waist circumference (WC) cm	99±10.12	118±11.10	125±15.12	0.03*
Leptin ng/mL	21.7±11.12	25.9±9.11	28.7±12.9	0.02*
Adiponectin µg/mL	4.88±2.01	4.2±1.15	3.6±1.01	0.03*
hs-CRP(mg/l)	18.8±5.17	24.9±10.13	26.6±9.16	0.04*
Fasting insulin (mIU/L)	6.4±2.33	6.9±2.41	8.9±3.64	>0.05

(Continued)

**Table 3** (Continued).

Parameters	Normal (18.5–25.0Kg/m <sup>2</sup> )	Overweight (25.0–29.9Kg/m <sup>2</sup> )	Obese (≥30.0Kg/m <sup>2</sup> )	P-value
Insulin Resistance (IR)	1.8±0.73	2.2±0.85	3.1±0.87	0.03*
Insulin Sensitivity (IS)	0.51±0.41	0.45±0.29	0.32±0.18	0.02*
AIP <sup>#</sup>				
Low Risk	8(34.8%)	10(16.1%)	2(3.1%)	>0.05
Middle Risk	11(47.8%)	22(35.5%)	27(41.5%)	0.05*
High Risk	4(17.4%)	30(48.4%)	36(55.4%)	0.05*

**Notes:** Data were expressed as the mean ± (SD) for continuous variables, P-value obtained one-way ANOVA. \*P≤0.05, and <sup>#</sup>AIP data was presented as numbers (%).

obese (7.93) BMI participants. Three tertiles also significantly differ in HDL-c, TG, and WC (P<0.05). The obese tertile had a higher average leptin level (28.7, P=0.02) than the other two tertiles, although adiponectin was lower (3.6, P=0.03). IR and hs-CRP are increased in obese people (3.1, 26.6, respectively). However, IS is lower in obese tertile than in the two categories. 55.4% of obese people had a greater AIP risk of CVD.

## The Correlation Between Leptin, Adiponectin, and Other Biomarkers in High HOMA-IR Index Tertile and High BMI (Obese Tertile)

**Table 4** shows leptin, adiponectin, and biological factor relationships. Leptin is linked strongly with HOMA-IR (P = 0.001). Leptin is associated favorably with FBG, TG, WC, hs-CRP, BMI, and AIP. An inverse correlation was found

**Table 4** Pearson's Correlation Coefficients Between Leptin, Adiponectin, and Another Factor

Parameters	Leptin		Adiponectin	
	r	P	r	P
FBG (mmol/L)	0.863	0.001**	<b>−0.661</b>	0.01*
HbA1c (%)	0.415	>0.05	<b>−0.611</b>	0.04*
LDL-c (mmol/L)	0.352	>0.05	0.332	>0.05
HDL-c (mmol/L)	<b>−0.617</b>	0.05*	0.627	0.04*
Total cholesterol (mmol/L)	0.413	0.06	0.423	0.07
Triglycerides (TG) (mmol/L)	0.852	0.02*	<b>−0.751</b>	0.04*
BMI (kg/m <sup>2</sup> )	0.635	0.03*	<b>−0.573</b>	0.05*
Waist circumference (WC) cm	0.321	>0.05	<b>−0.569</b>	0.05*
Fasting insulin (Uμ/mL)	0.422	0.07	0.321	0.06
Insulin Resistance (IR)	0.862	0.002**	<b>−0.642</b>	0.01*
Insulin Sensitivity (IS)	<b>−0.554</b>	0.02*	0.743	0.002**
hs-CRP (mg/l)	0.643	0.04*	0.313	>0.05
AIP	0.732	0.03*	<b>−0.652</b>	0.02*

**Notes:** P-values were obtained from Pearson's correlation. \* and \*\* indicate significance level at P≤0.05, and P≤0.001, respectively. Bold values indicate negative and inverse relation between leptin, adiponectin and other parameters.

between leptin and IS, HDL-c levels, with statistical significance ( $P=0.05$  and  $0.02$ , respectively). Adiponectin is linked adversely with HOMA-IR ( $P=0.002$ ). In addition, adiponectin is linked adversely with FBG, TG, WC, hs-CRP, BMI, and AIP. Adiponectin, IS, and HDL-c levels correlated positively ( $P=0.04$  and  $0.02$ , respectively).

## Multiple Linear Regression Analysis to Determine the Effects of Serum Leptin Level and Serum Adiponectin Level on T2DM Markers, Obesity Markers, and the Risk Factors for CVD in High HOMA-IR Index Tertile and High BMI (Obese Tertile)

**Table 5A** Model 1 focused on people with diabetes and employed leptin as an independent variable. The model summary showed that  $R^2=0.655$  explained 65.5% of the variation in IR, IS, BMI, HDL-c, and AIP levels from leptin. The coefficient table showed a significant connection between leptin levels and IR ( $B=5.98$ ,  $P=0.002$ ), BMI ( $B=3.89$ ,  $P=0.001$ ), and AIP ( $B=3.97$ ,  $P=0.02$ ),

**Table 5** Multiple Linear Regression Analysis to Determine the Effects of Serum Leptin Level (Model 1) and Serum Adiponectin Level (Model 2) on T2DM Markers, Obesity Markers, and the Risk Factors for CVD

Variables	95% CI	B	P value
Model 5A :Linear regression between Leptin and IR, IS, BMI, WC, and AIP among women with T2DM			
FBG (mmol/L)	1.964 to 5.104	4.365	0.003**
HDL-c (mmol/L)	−1.776 to −3.265	−2.854	0.02*
Triglycerides (TG) (mmol/L)	1.862 to 6.304	4.854	0.01*
BMI (kg/m2)	1.899 to 4.000	3.892	0.001**
Waist circumference (WC) cm	0.998 to 2.001	1.932	<0.001
Fasting insulin (Uμ/mL)	0.353 to 1.259	2.474	>0.05
Insulin Resistance (IR)	1.797 to 6.915	5.984	0.002**
Insulin Sensitivity (IS)	−2.997 to −7.205	−6.384	0.01*
hs-CRP (mg/l)	1.947 to 6.705	5.784	0.003**
AIP	1.392 to 4.055	3.974	0.02*
Adiponectin μg/mL	−1.219 to −5.150	−4.921	0.01*
R <sup>2</sup>		0.655	
Model 5B: Linear regression between Adiponectin and IR, IS, BMI, WC, AIP			
FBG (mmol/L)	−1.159 to −3.190	−2.892	0.01*
HDL-c (mmol/L)	2.946 to 5.604	4.832	0.04*
Triglycerides (TG) (mmol/L)	1.803 to 2.159	1.372	0.06
BMI (kg/m2)	−2.6604 to −6.175	−5.952	0.03*
Waist circumference (WC) cm	−1.838 to −3.309	−2.912	0.04*
Fasting insulin (Uμ/mL)	0.793 to 1.135	1.354	>0.05
Insulin Resistance (IR)	−1.050 to −4.009	−3.762	0.02*
Insulin Sensitivity (IS)	2.136 to 4.013	3.339	0.03*

(Continued)

**Table 5** (Continued).

Variables	95% CI	B	P value
hs-CRP (mg/l)	0.561 to 1.627	1.329	>0.05
AIP	−1.541 to −3.177	<b>−2.382</b>	0.04*
Leptin ng/mL	−1.219 to −5.150	<b>−4.921</b>	0.01*
R <sup>2</sup>		<b>0.643</b>	

**Notes:** Serum leptin and adiponectin levels were used as the independent variable along with several dependent variables in Multiple Linear Regression analysis. Unstandardized coefficients (B), and 95% confidence intervals (CIs) were statistically significant at  $P \leq 0.05^*$  or  $\leq 0.001^{**}$ . R<sup>2</sup>: coefficient of regression: Unstandardized Coefficients; Value of R<sup>2</sup> ranged from 0–1. Bold values indicate negative and inverse relationship between leptin and adiponectin.

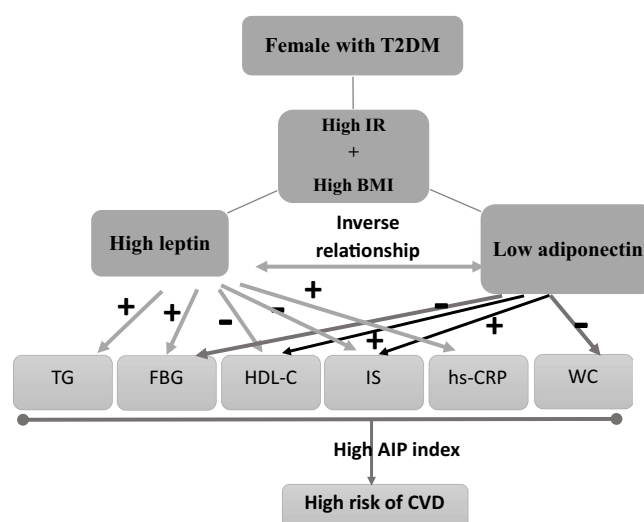
but not WC ( $P > 0.05$ ). However, leptin levels correlated negatively with IS ( $B = -6.38$ ,  $P = 0.01$ ) and HDL-c ( $B = -2.85$ ,  $P = 0.02$ ). Table 5B showed a significant relationship between adiponectin levels and IS and HDL-c ( $B = 3.33$ ,  $P = 0.03$ ,  $B = 4.83$ ,  $P = 0.04$ , respectively) when adiponectin was used as an independent variable in linear analysis (Model 2). However, the results of linear regression demonstrated a significant inverse relationship between adiponectin levels and IR ( $B = -3.76$ ,  $P = 0.02$ ), BMI ( $B = -5.95$ ,  $P = 0.03$ ), WC ( $B = -2.91$ ,  $P = 0.04$ ) and AIP ( $B = -2.38$ ,  $P = 0.04$ ) with  $R^2 = 0.643$ . Additionally, the result from linear regression proved a negative and inverse relationship between leptin and adiponectin levels in T2DM patients (Table 5).

## Discussion

IR is a key factor in the pathogenesis of obesity and T2DM, and several studies have shown a link between IR and adipose tissue indicators, including leptin and adiponectin.<sup>14–16</sup> Therefore, this research aims to examine how leptin and adiponectin levels affect IR, IS, BMI, WC, and AIP in Saudi women with T2DM. This is the first research on Saudi females that studied leptin and adiponectin levels in T2DM, including obesity and CVD risk factors.

## Relationship Between Leptin and Diabetes, Obesity, and the Risk of CVD

Table 1 shows that leptin and AIP index increased FBG, HbA1C, lipid levels, BMI, and hs-CRP. While the HOMA-IR index also increases similar indicators, Table 2. These results parallel the IR study, which is favorably linked with



**Figure 1** Schematic chart representation of the influences of high leptin and low adiponectin levels on major factors involved in the complications of T2DM, such as CVD in Saudi females with high insulin resistance (IR) and high body mass index (BMI), triglycerides (TG), fasting blood glucose (FBG), high-density lipoprotein-cholesterol (HDL-C), insulin sensitivity (IS), C-reactive protein (hs-CRP), and waist circumference (WC). (+) represented positive relation whereas (-) represented negative.



metabolic indicators.<sup>14–16</sup> Our study demonstrated that increasing leptin levels were substantially related to IR and other risk factors, such as triglycerides, FBG, and BMI, but inversely associated with HDL-c, a protective factor against IR.<sup>16</sup> It was discovered that leptin levels might predict IR. The linear regression analysis showed a statistically significant connection between leptin levels and IR in women with T2DM and impaired insulin sensitivity. Some studies show leptin plays a key role in the pathophysiology of IR.<sup>17,18</sup> Serum leptin rises with obesity, according to Guarino et al,<sup>17</sup> as it's linked to BMI and adiposity in women. However, our data showed that serum leptin concentrations in women increase with BMI and IR. BMI is the most important factor related to elevated blood leptin levels in women, according to many investigations.<sup>19</sup> These investigations found a favorable connection between serum leptin and triacylglycerol in women with a high BMI. This supports our findings. Leptin was linked with IR and BMI in diabetic women, although relationships depended on BMI. In another investigation, women's body mass, body fat mass, and blood leptin levels were also strongly correlated.<sup>20</sup> In women, subcutaneous abdominal adipocytes secrete three times more leptin than intra-abdominal fat. Subcutaneous adipocytes are the principal source of serum leptin,<sup>20</sup> which partly explains our participants' elevated leptin level due to their high WC and BMI.

Also, several researches have proven leptin's cardiovascular effects.<sup>21,22</sup> However, leptin's role in promoting CVD is still controversial. Many researchers support its role as a factor that stimulates inflammation, oxidative stress, atherogenesis, and thrombosis, consequently stimulating endothelial dysfunction, arterial stiffness, and atherosclerotic plaque development.<sup>23</sup> Raised leptin levels are linked to IR and T2DM.<sup>24</sup> In T2DM, high leptin levels increase CVD risk.<sup>25</sup> In T2DM patients with high leptin levels, obesity, hypertension, Metabolic syndrome MetS, and endothelial dysfunction are more prevalent.<sup>26,27</sup> The research found a favorable and direct association between high leptin and high AIP, a valuable indication for diagnosing CVD risk. Leptin levels increase the risk of CVD in T2DM women with high IR and obesity. In obesity, excessive fat buildup causes an increase in free fatty acids in adipose tissue, which raises triglyceride levels. Adipose tissue produces leptin, which regulates energy balance and weight. Leptin reduces lipid, fatty acid, and acetyl CoA carboxylase production, causing lipid buildup. HDL-c struggles to restrict triglyceride and cholesterol formation in the arteries, making atherosclerosis difficult to prevent.

The research found an association link between leptin and triglycerides in T2DM women with high IR but a negative relationship with HDL-c. Leptin increases triglycerides and reduces HDL-c, making it an independent risk factor for CVD. T2DM women exhibited high hs-CRP levels, which are linked with increased leptin. Higher hs-CRP is linked to a high global cardiovascular risk without baseline CVD. hs-CRP is useful in CVD risk assessment and promotes vascular inflammation, vessel damage, and clinical CVD events. It may also predict the long-term risk for myocardial infarction and fast cardiac mortality in healthy persons.<sup>28</sup> The study results indicated that leptin might be an independent risk factor for IR and CVD risk variables, such as raising triglyceride and hs-CRP levels and reducing HDL-c levels in T2DM and obese women.

## Relationship Between Adiponectin and Diabetes, Obesity, and the Risk of CVD

Table 1 shows that metabolic indicators increased, whereas adiponectin and HDL-c decreased. As HOMA-IR and BMI elevated, adiponectin levels fell (Table 2 and Table 3). Several clinical studies revealed that elevated adiponectin is a negative predictor of IR and T2DM in BMI-adjusted subjects,<sup>29,30</sup> and a low plasma adiponectin level may increase T2DM risk.<sup>31</sup> In agreement with these previous studies, the results showed a substantial negative association between adiponectin decrease and IR but a favorable link with IS. The linear regression analysis showed a significant negative correlation between adiponectin levels and high IR and BMI levels in females with T2DM. In obese people, visceral body fat may affect health owing to aberrant adipokine production. Adiponectin is essential for energy metabolism; its levels drop in obesity and increase following weight reduction.<sup>32,33</sup> Adiponectin is negatively related to BMI, glucose, insulin, triglyceride, IR, and visceral fat.<sup>32</sup> From lean to overweight to obese, adipose tissue enlarges. This changes leptin and adiponectin levels. Hypoadiponectinemia, inversely linked with fat mass, may connect obesity to CVD. Several human investigations have linked hypoadiponectinemia to cardiovascular problems.<sup>32,33</sup> Consistent with the mentioned studies, our findings showed that obese women with T2DM and low adiponectin and HDL-c were at elevated risk of CVD. Low adiponectin levels are highly connected with obesity-related cardiovascular illnesses, including ischemic heart disease and peripheral artery disease. Therefore, reduced adiponectin may cause IR, T2DM, and CVD.

## Relationship Between Leptin and Adiponectin

Leptin and adiponectin strongly associate with T2DM<sup>3,34</sup> and obesity, according to Liao et al and Lee et al.<sup>35,36</sup> The research found that IR individuals had lower adiponectin levels, and leptin increases with obesity in diabetic patients, although adiponectin decreases.<sup>37</sup> Wang et al found that adiponectin lowered blood leptin and IR.<sup>38</sup> These results align with multiple linear regression that showed a negative and inverse connection between leptin and adiponectin in T2DM women with high IR and BMI (obese female).

## Conclusion

This study presented better knowledge of the relationship between leptin, adiponectin, and the major factors involved in the complications of T2DM, such as CVD and obesity in Saudi females first time (Figure 1). In summary, the study revealed that IR, BMI, hs-CRP, TG, and AIP were the main factors associated positively with the raising in leptin levels in Saudi female diabetic patients, while HDL-c and IS were the major factors correlated positively with a reduction in adiponectin levels. In addition, the decrease in adiponectin levels is associated with a reduction in IS and HDL-c levels. Therefore, individuals with high leptin and low adiponectin levels should be monitored in T2DM obese females, and sufficient healthcare should be offered to prevent or reduce T2DM complications such as CVD. Moreover, there are certain limitations to our investigation when it comes to sampling size and gender; therefore, future research must compare the sexes on a large-scale basis.

## Research Summary

- IR, BMI, hs-CRP, TG, and AIP were the main factors associated positively with the raising in leptin levels in Saudi female diabetic patients, while HDL-c and IS were the major factors correlated positively with a reduction in adiponectin levels.
- Individuals with high leptin and low adiponectin levels should be monitored in T2DM obese females, and sufficient healthcare should be offered to prevent or reduce T2DM complications such as CVD.

## Abbreviations

IR, Insulin Resistance; DM, Diabetes Mellitus; (HOMA-IR Index), Homeostasis Model Assessment-Estimated Insulin Resistance; AIP, Atherogenic Index of Plasma; BMI, Body Mass Index; CVD, Cardiovascular Disease; ELISA, Enzyme-Linked Immunosorbent Assay; FBG, Fasting Blood Glucose; HbA1c, Hemoglobin A1c; HDL-C, High-Density Lipoprotein; Hs-CRP, High-Sensitivity C-Reactive Protein; IS, Insulin Sensitivity; LDL-C, Low-Density Lipoprotein Cholesterol; QUICKI, Quantitative Insulin Sensitivity Check Index; T2DM, Type 2 Diabetes Mellitus; TC, Total Cholesterol; TG, Triglycerides; WC, Waist Circumference.

## Data Sharing Statement

The dataset produced for this study is accessible on request to the corresponding author.

## Ethics Approval Statement

Ethical authorization to carry out the study was obtained from the Ethical Committee at the College of Applied Medical Sciences, Taibah University, Madinah, and the Institutional Review Board, General Directorate of Health Affairs in Madinah (IRB 022-22).

## Patient Consent Statement

All participants were priorly informed about the research and written informed consent were obtained by following the Helsinki guidelines and was accepted by the Ethical Committee at the College of Applied Medical Sciences, Taibah University.

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## Disclosure

The authors report no conflicts of interest in this work.

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