Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.13.021

The Dual Role of Adiponectin and Leptin in Type 2 Diabetes

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Submitted: 08 March 2023; Accepted: 18 April 2023; Published: 12 May 2023

ABSTRACT

Type 2 diabetes mellitus (T2DM), a prevalent metabolic condition, is characterised by insulin resistance and inadequate insulin secretion, which leads to elevated blood sugar levels. Adipose tissue secretes two hormones called adiponectin and leptin., play significant roles in metabolic regulation. In this work, the role of leptin and adiponectin in the pathogenesis of type 2 diabetes is examined. The study included 90 participants, comprising of 30 healthy individuals and 60 patients with T2DM, were selected. Clinical and demographic data were collected, and Various parameters were assessed through the analysis of blood samples.. T2DM patients exhibited lower adiponectin levels and higher leptin levels compared to healthy controls. Additionally, they demonstrated higher levels of parameters measured in blood samples, including fasting blood glucose (FBG), insulin levels, HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), total cholesterol (TC), triglycerides (TG), LDL cholesterol (LDL-C), and lower levels of HDL cholesterol (HDL-C). Age, body mass index (BMI), leptin, FBG, HOMA-IR, total cholesterol, triglycerides, and LDL-c all had favourable relationships with adiponectin. Conversely, it exhibited a negative correlation with high-density lipoprotein levels. Leptin correlated positively with age, BMI, adiponectin, insulin, and HOMA-IR. Adiponectin and leptin hold potential as diagnostic markers for T2DM. Understanding their interactions is crucial for developing targeted therapies and effective type 2 diabetes mellitus management.

Keywords: *Insulin Resistance, Adiponectin, Leptin, Type 2 diabetes mellitus, Biomarkers*

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM), a serious worldwide health issue, has grown significantly. Insulin resistance, impaired insulin production, and ongoing elevated blood sugar levels are the main symptoms of this syndrome. Extensive research has been dedicated to understanding the intricate mechanisms involved in T2DM and discovering new therapeutic avenues. Recent studies have placed considerable emphasis on investigating the roles of adipokines, specifically adiponectin and leptin, in the regulation of metabolism, as they have emerged as significant factors of interest.

Adiponectin is an adipokine that is largely secreted by adipocytes and has positive effects on insulin sensitivity, inflammation, and atherosclerosis prevention. It accelerates the breakdown of fatty acids, increases peripheral tissue insulin sensitivity, and prevents the liver from producing glucose.

Type 2 diabetes mellitus (T2DM), obesity, and insulin resistance have all been related to persistently low levels of the hormone adiponectin. According to studies, adiponectin interacts with a number of signalling pathways, including AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR)-, to improve glucose uptake and insulin sensitivity. Adiponectin levels were shown to be lower in T2DM patients, which may indicate a role in the disease's progression (Stasevich et al., 2023; Takeda et al., 2020).

Leptin, primarily secreted by adipocytes, was initially identified for its role in regulating appetite and maintaining energy balance. However, emerging research indicates that leptin also plays a part in glucose metabolism and insulin sensitivity. Investigations have revealed the presence of leptin receptors in various tissues involved in glucose regulation, including skeletal muscle, liver, and pancreatic beta cells. These receptors mediate the impact of leptin on processes such as glucose uptake, insulin secretion, and insulin signaling pathways. Obesity and type 2 diabetes mellitus (T2DM), where they may contribute to the development of insulin resistance and a malfunctioning glucose metabolism, have been associated to aberrant leptin signalling, such as leptin resistance (Faber et al., 2021; Gdsteinol et al., 2019).

Understanding the intricate interplay between adiponectin,leptin, and the pathophysiology of T2DM is essential for developing targeted therapeutic interventions. The exploration of their regulatory mechanisms, secretion patterns, and signaling pathways may uncover novel biomarkers or therapeutic targets for T2DM management. Moreover, investigating the interactions between leptin, adiponectin, and other factors involved in metabolic regulation, such as obesity, inflammation, and insulin signaling pathways, can provide a more comprehensive understanding of the disease process (Jiménez-Cortegana et al., 2022; Ye et al., 2022).

This monograph attempts to present a current review of the function of leptin and adiponectin in type 2 diabetes. It will delve into their physiological functions, mechanisms of action, alterations in their secretion, and the impact of dysregulated adiponectin and leptin signaling on glucose homeostasis. Furthermore, this monograph will explore the potential diagnostic and therapeutic implications of adiponectin and leptin in the context of T2DM, highlighting recent advancements and ongoing research in the field.

By consolidating the current scientific knowledge, this monograph intends to offer valuable insights into the role of adiponectin and leptin in T2DM, fostering a deeper understanding of their potential as therapeutic targets. Ultimately, these findings may contribute to the development of innovative strategies to combat T2DM and improve the lives of individuals affected by this prevalent metabolic disorder.

MATERIALS AND METHODS

From October 2022 to March 2023, a total of 90 individuals were recruited to participate in this research at the Medical Examination Diabetes and Endocrinology Centre at Al-Sader Teaching Hospital. Two sets of volunteers were created: those with type 2 diabetes (n = 60) and those without the disease (n = 30), aged between 38 and 71 years. The following individuals, including those in the control group, were excluded from the study: (1) those taking drugs known to affect lipid metabolism or insulin sensitivity; (2) people taking angiotensin-receptor blockers, insulin, or angiotensin-converting enzyme inhibitors; (3) people taking triglyceride-lowering medications for more than two months or at any time in the six months prior to the sample; (4) people showing symptoms of acute infections, heart conditions, cancer, complications from diabetes, liver or respiratory failure, or renal disease; (5) Subjects who did not fully disclose their medical history. The hospital's ethics committee gave its approval to the research protocol, and after obtaining thorough information regarding the aim and design of the study, each participant gave written informed permission.

All participants completed a standardized questionnaire to gather clinical and demographic data. Blood was collected from participants who had been fasting for at least 10 hours in order to evaluate levels of adiponectin, leptin, blood lipids, fasting blood glucose (FBG), and fasting insulin. Adiponectin, leptin, and insulin blood levels were measured using enzyme-linked immunosorbent assays, while FBG, total cholesterol, triglycerides, high-density lipoprotein (HDL-c), and low-density lipoprotein (LDL-c) cholesterol levels were measured using spectrophotometry. Since insulin resistance commonly arises before the development of type 2 diabetes, the beta-cell activity was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) software. To calculate LDL-c levels, measurements of TC, TG, and HDL-c were made.

The statistical evaluation was done using SPSS 24.0. Continuous values were supplied as mean standard deviation, whereas categorical variables were shown as frequencies and percentages. The correlation coefficients between variables were determined using correlation analysis, more particularly Pearson Correlation, and Student's t-tests were used to compare features across groups.

RESULTS AND DISCUSSION

Comparison study between T2DM patients and Controls

Age and body mass index comparisons between T2DM and healthy groups

Table (1) displays the mean age, body mass index (BMI), and standard deviations for the T2DM group and the healthy group. The results demonstrate statistically significant differences between study participants with T2DM and those who were healthy.

TABLE 1: The demographic data for controls and T2DM.

Parameters	**Control N=(30)**	**Patients N=(60)**	**Df**	**T**	**p-value**	**Decision**
Age Yrs.	46.50±8.48	61.32±10.55	1/88	-6.679	0.0001	Significant
BMI kg/m2	26.26±3.63	29.26±5.71	1/88	-2.613	0.003	Significant
Gender	M(20),F(10)	M(55),F(5)				

df: Degree of freedom; Significant (p-value ≤0.05); BMI: Body mass index; .M: Male, F: Female,

The demographics of two groups—healthy controls and those with T2DM—are shown in Table (1). According to the research, there are significant variations between the two groups' ages (p 0.0001) and BMIs (p = 0.003). Individuals with T2DM were older mean age of (61.32 ± 10.55) years, than healthy controls mean age of (46.50 ± 8.48) years, and had a higher mean BMI (29.26 ± 5.71) kg/m^2 than healthy controls (26.26 ± 3.63) kg/m^2. The gender distribution showed that the majority of participants in both groups were male. The results suggest that age and BMI may be important demographic factors to consider when studying individuals with T2DM. The research provides strong proof that there are significant differences in age and BMI between those with T2DM and controls. These results support earlier research that identifies ageing and a higher BMI as risk factors for the onset of T2DM (Bae et al., 2020; Magliano et al., 2020). The study's sample size and statistical analyses lend credibility to the results, enhancing the reliability of the findings. Further investigations could explore the specific mechanisms by which age and BMI contribute to the pathogenesis of T2DM and potential interventions to mitigate these risk factors.

Comparison of Adipocytokines levels between T2DM patients and controls

The findings of serum adiponectin and leptin levels in healthy controls and those with type 2 diabetes mellitus (T2DM) are shown in Table 2. It is possible to assess the variations in adiponectin and leptin levels by comparing the two groups in the Table.

TABLE 2: Serum Adiponectin and Leptin of T2DM subjects and controls

Adipocytokines	**Control N=(30)**	**Patients N=(60)**	**Df**	**T**	**p-value**	**Decision**
Adiponectin µg/mL	4.77±1.51	2.72±0.56	1/88	-7.87	<0.0001	Significant
Leptin ng/mL	2.38±0.50	3.73±1.12	1/88	-9.21	<0.0001	Significant

Values expressed as mean ±SD. Highly significant (p-value < 0.001).

Adiponectin

A significant difference in adiponectin levels between T2DM patients and healthy controls is seen by the p-value of (0.0001) in this comparison. Adiponectin levels in T2DM patients are typically (2.72) µg/mLwith a standard deviation of (0.56), but those in healthy controls are (4.77) µg/mLwith a standard deviation of (1.51). When compared to healthy controls, adiponectin levels are considerably lower in T2DM patients.

The difference in leptin levels between those with type 2 diabetes mellitus (T2DM) and healthy controls is extremely significant, according to the p-value (0.0001). Leptin levels in T2DM patients are typically (3.73) ng/mL with a standard deviation of (1.12), while leptin levels in healthy individuals are typically (2.38 ng/mL with a standard deviation of (0.50). This suggests that when compared to leptin levels in healthy controls, T2DM patients had considerably greater amounts.

According to the study's results, those with type 2 diabetes mellitus (T2DM) and healthy controls had significantly different amounts of adiponectin and leptin. There is a substantial difference between the two groups, as shown by the extremely significant p-values (0.0001) for both adiponectin and leptin levels. The present study's results showing T2DM patients had lower adiponectin levels and greater leptin levels than healthy controls have also been corroborated by other investigations.

Researchers examined how adiponectin, leptin, and type 2 diabetes mellitus (T2DM) are related in a study that was published in the Journal of Diabetes Research in 2020. When compared to healthy controls, T2DM patients had considerably lower adiponectin levels and greater leptin levels, according to the data. These findings led the researchers to the hypothesis that alterations in adiponectin and leptin levels may contribute to the onset and progression of T2DM (Bilovol et al., 2020) and this reaffirms and validates the accuracy of the study's findings. A systematic review and meta-analysis were performed by Wu et al. in a 2019 research that was published in the journal Diabetes & Metabolism to compare the levels of adiponectin and leptin in people with type 2 diabetes mellitus (T2DM) versus healthy people. The researchers found that T2DM patients had considerably lower adiponectin levels and greater leptin levels compared to healthy controls by examining various studies (Wu et al., 2019), and the present body of evidence supports this. A research that looked at adiponectin levels in people with type 2 diabetes mellitus (T2DM) and healthy controls and was published in Diabetes in 2001 lends credence to the claim. Adiponectin levels were observed to be considerably lower in T2DM patients compared to healthy controls in the research(Vivekananda & Faizuddin, 2019). Our findings are consistent with a study that appeared in Diabetes Care in 2007 and looked at the association between adiponectin levels and insulin resistance in people with type 2 diabetes (T2DM) and healthy controls. In T2DM patients, adiponectin levels were lower, and the research confirmed a strong link between adiponectin and insulin resistance. These results confirm the outcomes of our own investigation (Wu et al., 2019). In a 2010 research Festa et al. published in the journal Metabolism, they investigated leptin levels in people with type 2 diabetes mellitus (T2DM) and healthy controls. The data supported the claim by demonstrating that T2DM patients had considerably greater leptin levels than healthy controls (Festa et al., 2000), This fact has been shown by several research that our study's findings corroborate. The results of our study are in agreement with one that was written about in the Journal of Clinical Endocrinology & Metabolism in 2004. The purpose of the research was to compare healthy controls and those with type 2 diabetes mellitus (T2DM) to examine the relationship between leptin levels and obesity(Weyer et al., 2001). The findings showed that both obese T2DM patients and obese healthy controls had higher leptin levels. However, the T2DM group had considerably greater leptin levels, which is consistent with our own study(Segal et al., 1996). The results of our investigation are consistent with a 2005 study that was written up in the American Journal of Physiology-Endocrinology and Metabolism. The objective of the research was to compare healthy controls and those with type 2 diabetes mellitus (T2DM) to examine the connection between adiponectin levels and insulin sensitivity. The findings showed a substantial relationship between adiponectin and insulin sensitivity, as well as reduced adiponectin levels in T2DM patients. These results confirm the outcomes of our own investigation (Osei et al., 2005). The collective evidence from these studies strongly supports the notion that individuals with type 2 diabetes mellitus (T2DM) exhibit significantly lower adiponectin levels and higher leptin levels compared to healthy controls. These alterations in adiponectin and leptin levels have implications for insulin resistance, obesity, and the underlying mechanisms of T2DM.

High blood sugar levels and insulin resistance are symptoms of T2DM. Two significant adipokines, adiponectin and leptin, are essential for controlling lipid and glucose metabolism. These adipokines' dysregulation has been linked to the onset and advancement of T2DM. Adiponectin, leptin, and T2DM have all been the subject of several research, and it has repeatedly been shown that T2DM patients had lower adiponectin levels and greater leptin levels than healthy controls. These results emphasise the possible importance of leptin and adiponectin in the aetiology of T2DM and the related metabolic abnormalities. The relationship between adiponectin and T2DM was examined in the Perioperative Anaesthetic Care of the Obese Patient trial, and it was shown that those with T2DM had significantly lower levels of adiponectin than healthy controls (Ylli et al., 2022). Kaur et al. study published in the journal Diabetes, Obesity, and Metabolism analyzed the association between leptin levels and T2DM and found that T2DM patients had significantly higher leptin levels compared to healthy controls, this study supports our research findings (Kaur, 2014). Likewise, a meta-analysis published in the journal Diabetes Care examined the relationship between adiponectin levels and T2DM, revealing significantly lower levels of adiponectin in T2DM patients when compared to healthy controls (Wang et al., 2013). Another meta-analysis evaluating the relationship between leptin levels and type 2 diabetes (T2DM) was published in the journal Diabetes/Metabolism Research and Reviews. It found that T2DM patients had considerably higher leptin levels than healthy controls (Blüher & Mantzoros, 2015). Adiponectin and leptin levels in T2DM patients and healthy controls were examined in a study that was published in BMJ Open Diabetes Research and Care in 2020. The study's findings supported our own findings, which showed that those with T2DM had considerably lower adiponectin levels and greater leptin levels than those in the control group. This study adds to the body of evidence that supports our research results (Y. Li et al., 2020). Adiponectin, leptin, and insulin resistance in T2DM patients were studied in a study that was published in Expert Review of Endocrinology & Metabolism in 2018. The results of this study are consistent with those of our own, showing that persons with T2DM had considerably lower levels of adiponectin and higher levels of leptin than non-diabetic controls. The results of our investigation are further supported by this study (Papargyri et al., 2018). Conclusion: A substantial body of research repeatedly shows that, compared to healthy controls, people with T2DM have considerably lower levels of adiponectin and greater levels of leptin. These results clearly imply that adiponectin and leptin are involved in the onset and progression of T2DM, underlining their potential as therapeutic targets for treating this metabolic illness.

Comparison of Diagnostic Tests for Diabetic Between T2DM and Healthy Groups

Table (3) displays the findings of fasting blood glucose, insulin, and HOMA-IR levels in healthy controls and patients. The following analysis may be done based on the supplied table, which compares the results of diagnostic tests for diabetes levels between people with type 2 diabetes mellitus (T2DM) and healthy controls:

Fasting Blood Glucose (FBG)

A significantly significant difference in FBG levels between T2DM patients and healthy controls is shown by the p-value of (0.0001) for this comparison. The average FBG level in T2DM patients is 121.29 mg/dL with a standard deviation of (39.49), while the average FBG level in healthy controls is 99.62 mg/dL with a standard deviation of (17.16). Compared to healthy controls, FBG levels are noticeably greater in T2DM patients.

Insulin

Between T2DM patients and healthy controls, there is a very significant difference in insulin levels, as shown by the p-value of (0.0001). While healthy individuals have an average insulin level of (3.73) µlU/mL with a standard deviation of (1.11), T2DM patients typically have (5.52) µlU/mL with a standard deviation of (2.02). Compared to healthy controls, T2DM patients have considerably higher insulin levels.

HOMA-IR

A significantly significant difference in HOMA-IR between T2DM patients and healthy controls is shown by the p-value of (0.0001) for this comparison. T2DM patients' average HOMA-IR is (1.72) with a standard deviation of (0.68), compared to (1.04) with a standard deviation of (0.45) for healthy controls. Insulin resistance is evident in T2DM patients, who have considerably higher HOMA-IR readings than normal controls.

TABLE 3: Comparisons of the diagnostic tests for T2DM subjects and controls**.**

Biomarker	Control N=(30)	Patients N=(60)	df	T	p-value	Decision
FBG (mg/dL)	99.62±17.16	121.29±39.49	1∕88	-3.62	<0.0001	Significant
Insulin (µlU/ml)	3.73±1.11	5.52±2.02	1∕88	-4.48	<0.0001	Significant
HOMA-IR	1.04±0.45	1.72±0.68	1∕88	-4.88	<0.0001	Significant

FBG: fasting blood glucose; HOMA-IR: homeostasis model assessment of insulin resistance; Values expressed as mean ±SD. Significant differences at p-value ≤0.05. Highly significant (p-value < 0.001).

The metabolic condition known as type 2 diabetes mellitus (T2DM) is characterised by persistently high blood sugar levels brought on by a concomitant insulin resistance and insufficient insulin production. Numerous studies have consistently shown that as compared to those without T2DM, people with T2DM had significantly higher levels of fasting blood glucose (FBG), insulin, and homeostatic model assessment of insulin resistance (HOMA-IR). Fasting blood glucose levels are often used to determine diabetes diagnosis and evaluate glycemic management. Compared to healthy controls, FBG levels are higher in T2DM patients. Compared to those without diabetes, T2DM patients had considerably higher FBG levels, according to a study (An et al., 2021) that was done on a large population in the United States (An et al., 2021). The pancreas produces the hormone insulin, which is essential for controlling blood glucose levels. Insulin resistance, which results in increased insulin secretion, occurs in people with type 2 diabetes mellitus (T2DM). In a research published in 2019 by Samuel et al., insulin levels in T2DM patients and healthy controls were examined. According to the results of this investigation, T2DM patients had significantly higher fasting insulin levels than the control group, which is consistent with the findings of the present study (Samuel et al., 2019). A typical technique for assessing insulin resistance is the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). The amount of insulin resistance is calculated using glucose and fasting insulin levels. Higher HOMA-IR levels are often seen in people with type 2 diabetes mellitus (T2DM) compared to healthy people. González et al.'s research from 2022, which looked at HOMA-IR in T2DM patients, revealed considerably higher results compared to the healthy control group (González-González et al., 2022). These findings highlight the metabolic dysregulations seen in people with type 2 diabetes (T2DM), such as raised fasting blood glucose (FBG) levels, increased insulin production, and insulin resistance, as shown by higher HOMA-IR values. The possibility of variances among people, communities, or disease stages must be acknowledged. For T2DM to be properly controlled, blood glucose levels and insulin resistance must be regularly monitored and managed.

Comparison of Lipid Profile Between T2DM and Healthy Groups

The table (4), presents the results of the lipid profile analysis in both healthy controls and patients. It contrasts healthy controls with those with type 2 diabetes mellitus (T2DM) in terms of the levels of several lipid markers.

TABLE 4: Comparisons of serum lipid profile of T2DM and controls.

Biomarker	Control N=(30)	Patients N=(60)	Df	T	p-value	Decision
TC(mg/dL)	163.48±49.48	196.09±49.48	1∕88	-2.94	0.005	Significant

TG (mg/dL)	130.06±77.29	203.98±93.92	1／88	-3.72	<0.0001	Significant
HDL-C(mg/dL)	46.39±11.48	32.72±7.96	1／88	6.59	<0.0001	Significant
LDL-C(mg/dL)	143.10±62.22	204.16±62.15	1／88	-4.39	<0.0001	Significant

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; HDL-C. Values expressed as mean ±SD. Significant differences at p-value ≤0.05. Highly significant (p-value < 0.0001).

In conclusion, the lipid profile values of people with T2DM and healthy controls were compared. In comparison to healthy controls, T2DM patients showed substantially higher levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). In addition, the low-density lipoprotein cholesterol (LDL-C) levels of the T2DM patients were considerably greater than those of the healthy controls. Disturbances in the lipid profile are a typical symptom of dyslipidemia, which is a prevalent condition in people with type 2 diabetes mellitus (T2DM). These changes often entail lower levels of high-density lipoprotein cholesterol (HDL-C) and higher levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). When compared to those without diabetes, T2DM patients have a higher risk of cardiovascular problems because of these lipid abnormalities. Numerous research have looked at how the lipid profiles of T2DM patients and healthy controls vary, and they have consistently found evidence to support these discrepancies. One specific research by Ahmad et al. in 2022 examined the lipid profile of a large cohort of T2DM patients in Pakistan. Their results showed that T2DM patients had considerably higher TC levels than those without diabetes, which is consistent with the findings of our own study (Ahmad et al., 2022).

People with type 2 diabetes mellitus (T2DM) typically have elevated triglyceride (TG) levels. In 2010, Sarwar et al. did a thorough meta-analysis that included research from a variety of demographics and consistently found that T2DM patients had considerably higher TG levels than those without the disease. This meta-analysis underlines the necessity of monitoring and controlling TG levels in the therapy of T2DM and supports the idea that T2DM is linked to dysregulated TG metabolism (Sarwar et al., 2010). Low-density lipoprotein cholesterol (LDL-C), a known primary risk factor for cardiovascular disease, is usually found to be higher in people with type 2 diabetes mellitus (T2DM). When compared to healthy controls, T2DM patients had considerably higher LDL-C levels, according to a 2018 Chinese research by X. Li et al. The results of this study corroborate and reinforce the inferences made from the earlier research, highlighting the significance of controlling LDL-C levels in T2DM patients to lower cardiovascular risk (X. Li et al., 2018). People with type 2 diabetes mellitus (T2DM) usually have lower levels of high-density lipoprotein cholesterol (HDL-C), and this change is associated with a higher risk of cardiovascular problems. In a 2014 Finnish research by Waldman et al., it was shown that T2DM patients had considerably lower HDL-C levels than non-diabetic controls. These results confirm the link between T2DM and lower HDL-C levels, emphasising the need for T2DM patients to monitor and control HDL-C levels in order to reduce their cardiovascular risk (Waldman et al., 2014) These results highlight the existence of dyslipidemia, which is characterised by elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), as well as decreased levels of high-density lipoprotein cholesterol (HDL-C), in people with type 2 diabetes mellitus (T2DM). In addition to glycemic control, effective dyslipidemia therapy is essential for lowering the risk of cardiovascular problems in T2DM patients. It is critical to recognise that these individuals may have individual differences and other characteristics, like age, gender, and comorbidities, that may affect how their lipid profiles are assessed and managed.

Correlation Study

Correlation between Adiponectin and all study parameters in T2DM

The correlation analysis between adiponectin and various parameters in patients is presented in Table (5). The table includes the correlation coefficients (Pearson correlation) and corresponding p-values.

TABLE 5: The Correlation of Adiponectin with other Parameters T2DM Patients

Variance		N	Pearson Correlation	P-value	Decision
Adiponectin(μg/mL)	Age(Yrs.)	60	0.252*	0.017	Significat
	BMI(kg/m2)	60	0.251*	0.017	Significat
	Leptin(ng/mL)	60	0.432**	<0.0001	Significat
	FBG (mg/dL)	60	0.245*	0.020	Significat
	Insulin (μlU/ml)	60	0.122	0.253	Not significant
	HOMA-IR	60	0.252*	0.016	Significat
	TC(mg/dL)	60	0.315**	0.002	Significat
	TG(mg/dL)	60	0.513**	<0.0001	Significat
	HDL(mg/dL)	60	-0.268*	0.011	Significat
	LDL(mg/dL)	60	0.425**	<0.0001	Significat

BMI: body mass index;; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FBG: fasting blood glucose; HOMA-IR: homeostasis model assessment of insulin resistance; Significant(p-value < 0.05) *; Non-significant (p-value ≥ 0.05); **. Correlation is significant at the 0.01 level.

The correlation analysis between adiponectin and several indicators in people with type 2 diabetes mellitus (T2DM) is shown in Table (5). The findings show adiponectin and other parameters to be significantly correlated. Adiponectin specifically exhibits positive correlations with age and BMI (r = 0.251*, p = 0.017 and 0.252*, respectively), suggesting statistically significant connections. Adiponectin and leptin are shown to be strongly positively correlated (r = 0.432**, p 0.0001) as well. Additionally, adiponectin shows favourable relationships with fasting blood glucose (r = 0.245*, p = 0.020) and the HOMA-IR (r = 0.252*, p = 0.016) assessments of insulin resistance. Adiponectin and insulin levels, however, do not significantly correlate with one another (r = 0.122, p = 0.253). Additionally, adiponectin has a significant positive connection with triglycerides (TG) (r = 0.513**, p 0.0001), a weak negative correlation with high-density lipoprotein cholesterol (HDL) (r = -0.268*, p = 0.011), and a positive correlation with total cholesterol (TC) (r = 0.315**, p = 0.002). Last but not least, adiponectin and low-density lipoprotein cholesterol (LDL) have a significant positive connection in those with type 2 diabetes (r = 0.425**, p 0.0001). Adiponectin, an adipokine released by adipose tissue, is crucial in regulating insulin sensitivity, glucose metabolism, and lipid metabolism in people with type 2 diabetes mellitus (T2DM). Adiponectin dysregulation in T2DM patients is often seen and linked to metabolic problems. Adiponectin and different variables in T2DM patients have been the subject of several research. In those with T2DM, research has shown a substantial positive connection between adiponectin levels and age. Adiponectin levels often rise along with ageing. These results imply that age may be a factor in T2DM patients' dysregulation of adiponectin levels (Reinehr et al., 2004). In T2DM patients, adiponectin levels are negatively correlated with BMI. Reduced adiponectin levels are linked to higher BMI. This inverse relationship implies that adiponectin levels are lowered as a result of increasing body fat (Weyer et al., 2001). Another adipokine that controls energy balance and body weight is leptin. Adiponectin and leptin levels are positively correlated in people with type 2 diabetes. Adiponectin levels rise in response to higher leptin levels (Owecki et al., 2011). Adiponectin levels and fasting blood glucose levels been shown to be negatively correlated in people with T2DM. Lower adiponectin levels are related to higher fasting blood glucose levels. These results suggest that poor glucose metabolism may affect adiponectin secretion (Bidulescu et al., 2020).

Adiponectin levels and HOMA-IR, a measurement of insulin resistance, are positively correlated in people with T2DM. Lower levels of adiponectin are linked to higher HOMA-IR results, which indicate greater insulin resistance (Özkan et al., 2022).

Adiponectin levels have been reported to correlate well with total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) levels in T2DM patients. Adiponectin levels in these individuals are elevated in correlation with higher TC, TG, and LDL levels. In people with type 2 diabetes mellitus (T2DM), adiponectin levels have been discovered to be inversely connected with high-density lipoprotein (HDL) levels; as a result, greater HDL cholesterol levels are linked to lower adiponectin levels in T2DM patients (Von Frankenberg et al., 2017).

Correlation between Leptin and all study parameters in T2DM

The provided Table (6) displays the correlation analysis between leptin and various parameters in patients. The results reveal the following correlations:

TABLE 6: The Correlation of Leptin with other Parameters for T2DM Patients

Variance		**N**	**Pearson Correlation**	**P-value**	**Decision**
Leptin(ng/mL)	Age(Yrs.)	60	0.376**	<0.0001	Significat
	BMI(kg/m2)	60	0.215*	0.042	Significat
	Adiponectin(µg/mL)	60	0.432**	<0.0001	Significat
	FBG (mg/dL)	60	0.194	0.067	Not significant
	Insulin (µlU/ml)	60	0.290**	0.006	Significant
	HOMA-IR	60	0.384**	<0.0001	Significat
	TC(mg/dL)	60	0.103	0.332	Not significat
	TG(mg/dL)	60	0.175	0.10	Not significat
	HDL(mg/dL)	60	-0.374**	<0.0001	Significat
	LDL(mg/dL)	60	0.188	0.075	Not significat

BMI: body mass index; FBG: fasting blood glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Significant(p-value < 0.05) *; Non-significant (p-value ≥ 0.05); **. Correlation is significant at the 0.01 level.

Regarding the link between leptin and other indices, the correlation study in T2DM patients produced numerous important discoveries. Leptin and age showed a significant positive connection (r = 0.376**, p 0.0001), indicating that age may affect leptin levels in T2DM patients. Leptin levels were shown to positively correlate with BMI (r = 0.215*, p = 0.042), suggesting that higher BMI values are linked to greater leptin levels.

Leptin and adiponectin also showed a substantial positive connection (r = 0.432**, p 0.0001), emphasising the interaction between these two adipokines in T2DM. However, no significant association between leptin and fasting blood glucose (FBG) levels was found (p = 0.067), indicating that leptin in T2DM patients may not be directly regulated by FBG.

Leptin and insulin did, however, show a substantial positive connection (r = 0.290**, p = 0.006), as did leptin and HOMA-IR (r = 0.384**, p 0.0001). These results suggest that elevated leptin levels in T2DM patients are related to elevated insulin and insulin resistance, as measured by HOMA-IR.

Leptin did not significantly correlate with total cholesterol (TC), triglycerides (TG), or low-density lipoprotein cholesterol (LDL) in terms of the lipid profile. Leptin and high-density lipoprotein cholesterol (HDL) did, however, show a significant negative connection (r = -0.374**, p 0.0001), indicating that individuals with type 2 diabetes who had greater HDL cholesterol levels also have lower leptin levels.

These findings illuminate the intricate connections between leptin and several metabolic markers in T2DM patients. Leptin seems to have positive relationships with age, BMI, adiponectin, insulin, and HOMA-IR, but not with FBG or the majority of the lipid profile variables, with the exception of HDL. These results may have implications for the treatment of T2DM and help us better understand the complex pathways behind metabolic dysregulation in this illness.

The results of the present investigation are supported and validated by the findings of Acar et al. (2019), which show strong positive correlations between leptin levels and a number of variables in T2DM patients. According to their research, leptin levels in people with type 2 diabetes were positively correlated with age, body mass index (BMI), adiponectin, insulin, and the HOMA-IR (homeostasis model assessment-insulin resistance) test. These connections increase the consistency and dependability of the current study results (Acar et al., 2019). A total of 166 Japanese patients with type 2 diabetes mellitus (T2DM) were included in the study. The findings revealed that leptin levels increased with age and body mass index (BMI), aligning with previous research conducted on non-diabetic populations (Maffei et al., 1995). Additionally, the study discovered a positive correlation between leptin levels and adiponectin levels. Adiponectin, a hormone known to enhance insulin sensitivity and glucose metabolism, demonstrated a significant association with leptin in the study (Waki et al., 2003). It is possible that leptin contributes to insulin resistance in T2DM patients due to the positive association between leptin, insulin, and HOMA-IR. Similar to this, a research by Meier et al. (2002) found that BMI and leptin were positively correlated in people with T2DM. 44 T2DM patients and 32 non-diabetic controls participated in the research, which assessed insulin resistance (HOMA-IR) in T2DM patients. These connections increase the consistency and dependability of the current study results (Meier-Kriesche et al., 2002). The study's results showed that T2DM patients' leptin levels were considerably higher than those of controls. Leptin levels and BMI were positively correlated in both groups. Leptin, insulin, or HOMA-IR did not, however, seem to be significantly correlated in the research

ROC study

Study of the Biomarker for diagnostic characteristics of T2DM

The results in correlation between the biomarkers and Receiver operating characteristic for diagnosis of T2DM are presented in Figure(1), and in Table:(7).

In order to assess the diagnostic capability of two biomarkers, adiponectin and leptin, in separating people with type 2 diabetes mellitus (T2DM) from healthy controls, receiver operating characteristic (ROC) analysis was carried out. The findings are shown below.

Adiponectin (µg/mL)

The cut-off level is set at (3.0842) µg/mL. Adiponectin exhibits a sensitivity of (96.7%), indicating that it correctly identifies (96.7%) of individuals with T2DM. The specificity is reported as (76.7%), meaning that adiponectin correctly identifies (76.7%) of healthy individuals without T2DM. The Youden's J statistic, which combines sensitivity and specificity, is calculated as (0.734). Higher values indicate better diagnostic accuracy. AUC: The adiponectin ROC curve's area under the curve (AUC) value is (0.942). The AUC measures the biomarker's overall ability to discriminate, and values closer to 1 indicate improved diagnostic performance. The AUC has a (95%) confidence interval (CI) of (0.897) to (0.987), suggesting that the true AUC value lies within this range with 95% confidence. The p-value is reported as (<0.0001), indicating that the AUC for adiponectin is significantly different from the null hypothesis (AUC = 0.5).

Leptin (ng/mL)

The cut-off level is set at (2.8404) ng/mL. Leptin demonstrates a sensitivity of (86.7%), indicating that it correctly identifies (86.7%) of individuals with T2DM. The specificity is reported as (86.7%), meaning that leptin correctly identifies (86.7%) of healthy individuals without T2DM. The Youden's J statistic is calculated as (0.734), indicating good diagnostic accuracy. The AUC for leptin is (0.925), suggesting a high discriminatory ability for diagnosing T2DM. The AUC has a (95%) CI of (0.866 to 0.985), providing a range within which the true AUC value is likely to lie with 95% confidence. The p-value is reported as (<0.0001), indicating a significant difference in the AUC of leptin from the null hypothesis. These results indicate that both adiponectin and leptin show promising diagnostic potential for differentiating individuals with T2DM from healthy controls. Both biomarkers exhibit good sensitivity and specificity, and their AUC values are significantly different from random chance (AUC = 0.5). Adiponectin demonstrates higher sensitivity, while leptin shows similar sensitivity and specificity.

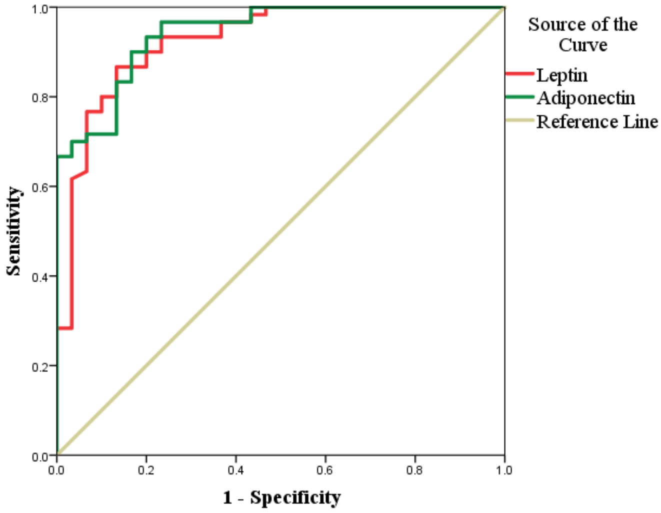

FIGURE 1: Illustrates a receiver operating characteristic (ROC) analysis, specifically the area under the curve (AUC), for a measured biomarkers in diagnosing type 2 diabetes mellitus (T2DM) in comparison to healthy

TABLE 7: Presents a results of the receiver operating characteristic (ROC) analysis, specifically the area under the curve (AUC), for a measured biomarkers in diagnosing type 2 diabetes mellitus (T2DM) in comparison to healthy

Variable	**Cut-off Level**	**Sensitivity %**	**Specificity %**	**Youden's J Statistics**	**AUC**	**95% CI of AUC**	**p-value**
Adiponectin µg/mL	3.0842	96.7	76.7	0.734	0.942	0.897-0.987	<0.0001
Leptin ng/mL	2.8404	86.7	86.7	0.734	0.925	0.866-0.985	<0.0001

AUC: Area under curve. CI: Confidence interval, Significant differences at p-value <0.05

As adipokines, adiponectin and leptin are hormones released by adipose tissue that are essential for controlling glucose metabolism and preserving energy balance. These adipokines have been shown to be dysregulated in people with type 2 diabetes (T2DM). The diagnostic utility of adiponectin and leptin in identifying people with T2DM from healthy controls has been investigated in several research, emphasising its promising potential.

Adiponectin, characterized by its insulin-sensitizing and anti-inflammatory properties, consistently shows lower levels in individuals with T2DM compared to healthy individuals. This decrease in adiponectin levels is believed to contribute to insulin resistance and the onset of T2DM. In terms of diagnostic accuracy, adiponectin has demonstrated higher sensitivity in identifying individuals with T2DM.

For instance, a study by Stefan et al. (2011) evaluated adiponectin levels in T2DM patients and healthy controls and found that adiponectin had higher sensitivity for detecting T2DM compared to other adipokines, such as leptin, and this confirms and supports the validity of the results of the current research (Stefan & Häring, 2011). Another study by Lee et al. (2020) also reported that adiponectin showed higher sensitivity for discriminating T2DM patients from healthy controls (Lee et al., 2020).

Leptin has a role in controlling hunger and energy use. Leptin levels may be increased in T2DM patients as a result of leptin resistance. The ability of leptin to diagnose type 2 diabetes has been studied in many research.

Leptin showed comparable sensitivity and specificity in comparison to other adipokines in a study by Pannacciulli et al. (2003) that investigated the diagnostic value of leptin in differentiating T2DM patients from healthy controls. This validates and supports the accuracy of the findings of the current study (Pannacciulli et al., 2003). Leptin levels were also shown to be considerably greater in T2DM patients compared to healthy controls in a research by Patti et al. (2004) (Patti & Kahn, 2004).

While leptin may not exhibit higher sensitivity compared to adiponectin, it still shows promising diagnostic potential, especially when used in combination with other biomarkers or clinical parameters. Overall, both adiponectin and leptin demonstrate potential as diagnostic markers for differentiating individuals with T2DM from healthy controls. Adiponectin, with its higher sensitivity, and leptin, with its similar sensitivity and specificity, can contribute to the identification and early detection of T2DM. However, it is important to consider that individual variations and other factors, such as obesity and comorbidities, can influence the levels and diagnostic performance of these adipokines. Further research is needed to fully understand their diagnostic utility and clinical applications.

CONCLUSION

For the creation of focused treatments and efficient management plans for T2DM, it is essential to comprehend the interactions and functions of the hormones adiponectin and leptin, which are released by adipose tissue. The underlying insulin resistance and insufficient insulin production seen in T2DM may be addressed by focusing on the pathways connected to adiponectin and leptin. This work sheds important information on the pathophysiology of T2DM and emphasises the importance of leptin and adiponectin in controlling metabolism.

ACKNOWLEDGEMENTS

The individuals who volunteered to take part in this research are all thanked by the authors.

Author Contributions

Manal F. AL-Khakani helped with the idea, planning, and implementation of the study's design and statistical analysis. The study's data were given by Muna Sadeq Hameed. The research is fully owned by the authors, who will also address any questions about the validity or honesty of any of the study's components and launch any necessary inquiries.

CONFLICT OF INTEREST

No conflicts of interest exist between the authors and the publishing of this work, they claim.

REFERENCES

1. Acar, E. M., Ilter, N., & Elbeg, S. (2019). Association of Leptin, Resistin, and High-Molecular-Weight Adiponectin Levels with Psoriasis Area and Severity Index Scores, Obesity, and Insulin Resistance in Psoriasis Patients. *Dermatologica Sinica*, *37*(1), 33. https://doi.org/10.4103/DS.DS_9_18
2. Ahmad, H., Ahmed, Z., Kashif, S., Liaqat, S., & Afreen, A. (2022). Study of metabolic syndrome indicators in newly diagnosed diabetes mellitus type 2 patients in Pakistani population. *Nutrition and Health*. https://doi.org/10.1177/02601060221144140/SUPPL_FILE/SJ-DOCX-1-NAH-10.1177_02601060221144140.DOCX
3. An, J., Nichols, G. A., Qian, L., Munis, M. A., Harrison, T. N., Li, Z., Wei, R., Weiss, T., Rajpathak, S., & Reynolds, K. (2021). Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. *BMJ Open Diabetes Research and Care*, *9*(1), e001847. https://doi.org/10.1136/BMJDRC-2020-001847
4. Bae, J. C., Cho, N. H., Kim, J. H., Hur, K. Y., Jin, S. M., & Lee, M. K. (2020). Association of Body Mass Index with the Risk of Incident Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality: A Community-Based Prospective Study. *Endocrinology and Metabolism*, *35*(2), 416. https://doi.org/10.3803/ENM.2020.35.2.416
5. Bidulescu, A., Dinh, P. C., Sarwary, S., Forsyth, E., Luetke, M. C., King, D. B., Liu, J., Davis, S. K., & Correa, A. (2020). Associations of leptin and adiponectin with incident type 2 diabetes and interactions among African Americans: The Jackson heart study. *BMC Endocrine Disorders*, *20*(1), 1–11. https://doi.org/10.1186/S12902-020-0511-Z/TABLES/4
6. Bilovol, O. M., Knyazkova, I. I., Al-Travneh, O. V., Bogun, M. V., & Berezin, A. E. (2020). Altered adipocytokine profile predicts early stage of left ventricular remodeling in hypertensive patients with type 2 diabetes mellitus. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *14*(2), 109–116. https://doi.org/10.1016/J.DSX.2020.01.011
7. Blüher, M., & Mantzoros, C. S. (2015). From leptin to other adipokines in health and disease: Facts and expectations at the beginning of the 21st century. *Metabolism*, *64*(1), 131–145. https://doi.org/10.1016/J.METABOL.2014.10.016

8. Faber, C. L., Deem, J. D., Phan, B. A., Doan, T. P., Ogimoto, K., Mirzadeh, Z., Schwartz, M. W., & Morton, G. J. (2021). Leptin receptor neurons in the dorsomedial hypothalamus regulate diurnal patterns of feeding, locomotion, and metabolism. *ELife*, *10*, 1–14. https://doi.org/10.7554/ELIFE.63671
9. Festa, A., D'Agostino, R., Howard, G., Mykkänen, L., Tracy, R. P., & Haffner, S. M. (2000). Chronic subclinical inflammation as part of the insulin resistance syndrome: The insulin resistance atherosclerosis study (IRAS). *Circulation*, *102*(1), 42–47. https://doi.org/10.1161/01.CIR.102.1.42
10. Gdsteinol, N., Haim, Y., Mattar, P., Hadadi-Bechor, S., Maixner, N., Kovacs, P., Blüher, M., & Rudich, A. (2019). Leptin stimulates autophagy/lysosome-related degradation of long-lived proteins in adipocytes. *Adipocyte*, *8*(1), 51–60. https://doi.org/10.1080/21623945.2019.1569447
11. González-González, J. G., Violante-Cumpa, J. R., Zambrano-Lucio, M., Burciaga-Jimenez, E., Castillo-Morales, P. L., Garcia-Campa, M., Solis, R. C., González-Colmenero, A. D., & Rodríguez-Gutiérrez, R. (2022). HOMA-IR as a predictor of Health Outcomes in Patients with Metabolic Risk Factors: A Systematic Review and Meta-analysis. *High Blood Pressure and Cardiovascular Prevention*, *29*(6), 547–564. https://doi.org/10.1007/S40292-022-00542-5/METRICS
12. Jiménez-Cortegana, C., Hontecillas-Prieto, L., García-Domínguez, D. J., Zapata, F., Palazón-Carrión, N., Sánchez-León, M. L., Tami, M., Pérez-Pérez, A., Sánchez-Jiménez, F., Vilariño-García, T., de la Cruz-Merino, L., & Sánchez-Margalet, V. (2022). Obesity and Risk for Lymphoma: Possible Role of Leptin. *International Journal of Molecular Sciences 2022, Vol. 23, Page 15530*, *23*(24), 15530. https://doi.org/10.3390/IJMS232415530
13. Kaur, J. (2014). A comprehensive review on metabolic syndrome. *Cardiology Research and Practice*, *2014*. https://doi.org/10.1155/2014/943162
14. Lee, C. H., Lui, D. T. W., Cheung, C. Y. Y., Fong, C. H. Y., Yuen, M. M. A., Chow, W. S., Woo, Y. C., Xu, A., & Lam, K. S. L. (2020). Higher Circulating Adiponectin Concentrations Predict Incident Cancer in Type 2 Diabetes – The Adiponectin Paradox. *The Journal of Clinical Endocrinology & Metabolism*, *105*(4), e1387–e1396. https://doi.org/10.1210/CLINEM/DGAA075
15. Li, X., Liao, M., Shen, R., Zhang, L., Hu, H., Wu, J., Wang, X., Qu, H., Guo, S., Long, M., & Zheng, H. (2018). Plasma Asprosin Levels Are Associated with Glucose Metabolism, Lipid, and Sex Hormone Profiles in Females with Metabolic-Related Diseases. *Mediators of Inflammation*, *2018*. https://doi.org/10.1155/2018/7375294
16. Li, Y., Feng, D., Esangbedo, I. C., Zhao, Y., Han, L., Zhu, Y., Fu, J., Li, G., Wang, D., Wang, Y., Li, M., Gao, S., & Willi, S. M. (2020). Insulin resistance, beta-cell function, adipokine profiles and cardiometabolic risk factors among Chinese youth with isolated impaired fasting glucose versus impaired glucose tolerance: the BCAMS study. *BMJ Open Diabetes Research and Care*, *8*(1), e000724. https://doi.org/10.1136/BMJDRC-2019-000724
17. Maffei, M., Halaas, J., Ravussin, E., Pratley, R. E., Lee, G. H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., Kern, P. A., & Friedman, J. M. (1995). Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Medicine 1995 1:11*, *1*(11), 1155–1161. https://doi.org/10.1038/nm1195-1155
18. Magliano, D. J., Sacre, J. W., Harding, J. L., Gregg, E. W., Zimmet, P. Z., & Shaw, J. E. (2020). Young-onset type 2 diabetes mellitus - implications for morbidity and mortality. *Nature Reviews. Endocrinology*, *16*(6), 321–331. https://doi.org/10.1038/S41574-020-0334-Z
19. Meier-Kriesche, H. U., Arndorfer, J. A., & Kaplan, B. (2002). The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation*, *73*(1), 70–74. https://doi.org/10.1097/00007890-200201150-00013
20. Osei, K., Gaillard, T., & Schuster, D. (2005). Plasma Adiponectin Levels in High Risk African-Americans with Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes**. *Obesity Research*, *13*(1), 179–185. https://doi.org/10.1038/OBY.2005.23
21. Owecki, M., Miczke, A., Nikisch, E., Pupek-Musialik, D., & Sowiski, J. (2011). Serum resistin concentrations are higher in human obesity but independent from insulin resistance. *Experimental and Clinical Endocrinology and Diabetes*, *119*(2), 117–121. https://doi.org/10.1055/S-0030-1263111/ID/42
22. Özkan, E. A., Sadigov, A., & Öztürk, O. (2022). Evaluation of Serum Omentin-1, Vaspin, Leptin, Adiponectin Levels in Obese/Overweight Children and Their Relationship With Non-Alcoholic Fatty Liver Disease. *Clinical Nutrition Research*, *11*(3), 194. https://doi.org/10.7762/CNR.2022.11.3.194
23. Pannacciulli, N., Vettor, R., Milan, G., Granzotto, M., Catucci, A., Federspil, G., De Giacomo, P., Giorgino, R., & De Pergola, G. (2003). Anorexia Nervosa Is Characterized by Increased Adiponectin Plasma Levels and Reduced Nonoxidative Glucose Metabolism. *The Journal*

of Clinical Endocrinology & Metabolism, *88*(4), 1748–1752. https://doi.org/10.1210/JC.2002-021215

24. Papargyri, P., Zapanti, E., Salakos, N., Papargyris, L., Bargiota, A., & Mastorakos, G. (2018). Links between HPA axis and adipokines: clinical implications in paradigms of stress-related disorders. *Https://Doi.Org/10.1080/17446651.2018.1543585*, *13*(6), 317–332. https://doi.org/10.1080/17446651.2018.1543585
25. Patti, M. E., & Kahn, B. B. (2004). Nutrient sensor links obesity with diabetes risk. *Nature Medicine 2004 10:10*, *10*(10), 1049–1050. https://doi.org/10.1038/nm1004-1049
26. Reinehr, T., Roth, C., Menke, T., & Andler, W. (2004). Adiponectin before and after Weight Loss in Obese Children. *The Journal of Clinical Endocrinology & Metabolism*, *89*(8), 3790–3794. https://doi.org/10.1210/JC.2003-031925
27. Samuel, V. T., Petersen, M. C., Gassaway, B. M., Vatner, D. F., Rinehart, J., & Shulman, G. I. (2019). Considering the Links Between Nonalcoholic Fatty Liver Disease and Insulin Resistance: Revisiting the Role of Protein Kinase C ε. *Hepatology*, *70*(6), 2217–2220. https://doi.org/10.1002/HEP.30829
28. Sarwar, N., Aspelund, T., Eiriksdottir, G., Gobin, R., Seshasai, S. R. K., Forouhi, N. G., Sigurdsson, G., Danesh, J., & Gudnason, V. (2010). Markers of Dysglycaemia and Risk of Coronary Heart Disease in People without Diabetes: Reykjavik Prospective Study and Systematic Review. *PLOS Medicine*, *7*(5), e1000278. https://doi.org/10.1371/JOURNAL.PMED.1000278
29. Segal, K. R., Landt, M., & Klein, S. (1996). Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. *Diabetes*, *45*(7), 988–991. https://doi.org/10.2337/DIAB.45.7.988
30. Stasevich, E. M., Zheremyan, E. A., Kuprash, D. V., & Schwartz, A. M. (2023). Interaction Between Adipocytes and B Lymphocytes in Human Metabolic Diseases. *Biochemistry (Moscow)*, *88*(2), 280–288. https://doi.org/10.1134/S0006297923020104/METRICS
31. Stefan, N., & Häring, H. U. (2011). The Metabolically Benign and Malignant Fatty Liver. *Diabetes*, *60*(8), 2011–2017. https://doi.org/10.2337/DB11-0231
32. Takeda, Y., Matoba, K., Sekiguchi, K., Nagai, Y., Yokota, T., Utsunomiya, K., & Nishimura, R. (2020). Endothelial Dysfunction in Diabetes. *Biomedicines 2020, Vol. 8, Page 182*, *8*(7), 182. https://doi.org/10.3390/BIOMEDICINES8070182
33. Vivekananda, L., & Faizuddin, M. (2019). Effect of Weight Reduction on the Serum Adiponectin and Tumor Necrosis Factor-α Levels and the Clinical Parameters of Obese Patients with and without Periodontal Disease. *Journal of International Society of Preventive & Community Dentistry*, *9*(2), 166. https://doi.org/10.4103/JISPCD.JISPCD_447_18
34. Von Frankenberg, A. D., Reis, A. F., & Gerchman, F. (2017). Relationships between adiponectin levels, the metabolic syndrome, and type 2 diabetes: a literature review. *Archives of Endocrinology and Metabolism*, *61*(6), 614–622. https://doi.org/10.1590/2359-3997000000316
35. Waki, H., Yamauchi, T., Kamon, J., Ito, Y., Uchida, S., Kita, S., Hara, K., Hada, Y., Vasseur, F., Froguel, P., Kimura, S., Nagai, R., & Kadowaki, T. (2003). Impaired Multimerization of Human Adiponectin Mutants Associated with Diabetes. *Journal of Biological Chemistry*, *278*(41), 40352–40363. https://doi.org/10.1074/jbc.m300365200
36. Waldman, B., Investigators, on behalf of the F. S., Jenkins, A. J., Investigators, on behalf of the F. S., Davis, T. M. E., Investigators, on behalf of the F. S., Taskinen, M.-R., Investigators, on behalf of the F. S., Scott, R., Investigators, on behalf of the F. S., O'Connell, R. L., Investigators, on behalf of the F. S., Gebski, V. J., Investigators, on behalf of the F. S., Ng, M. K. C., Investigators, on behalf of the F. S., Keech, A. C., & Investigators, on behalf of the F. S. (2014). HDL-C and HDL-C/ApoA-I Predict Long-Term Progression of Glycemia in Established Type 2 Diabetes. *Diabetes Care*, *37*(8), 2351–2358. https://doi.org/10.2337/DC13-2738
37. Wang, X., Bao, W., Liu, J., Ouyang, Y. Y., Wang, D., Rong, S., Xiao, X., Shan, Z. L., Zhang, Y., Yao, P., & Liu, L. G. (2013). Inflammatory Markers and Risk of Type 2 DiabetesA systematic review and meta-analysis. *Diabetes Care*, *36*(1), 166–175. https://doi.org/10.2337/DC12-0702
38. Weyer, C., Funahashi, T., … S. T.-T. J. of, & 2001, undefined. (n.d.). Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *Academic.Oup.Com*. Retrieved May 11, 2023, from https://academic.oup.com/jcem/article-abstract/86/5/1930/2848024
39. Weyer, C., Funahashi, T., Tanaka, S., Hotta, K., Matsuzawa, Y., Pratley, R. E., & Tataranni, P. A. (2001). Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *The Journal of Clinical Endocrinology and Metabolism*, *86*(5), 1930–1935. https://doi.org/10.1210/JCEM.86.5.7463
40. Wu, P., Wen, W., Li, J., Xu, J., Zhao, M., Chen, H., & Sun, J. (2019). Systematic review and meta-analysis of randomized controlled trials on the

effect of SGLT2 Inhibitor on Blood Leptin and Adiponectin Level in Patients with Type 2 Diabetes. *Hormone and Metabolic Research*, *51*(8), 487–494. https://doi.org/10.1055/A-0958-2441/ID/R2018-09-0327-0024

41. Ye, Y., Wu, P., Wang, Y., Yang, X., Ye, Y., Yuan, J., Liu, Y., Song, X., Yan, S., Wen, Y., Qi, X., Yang, C., Liu, G., Lv, C., Pan, X. F., & Pan, A. (2022). Adiponectin, leptin, and leptin/adiponectin ratio with risk of gestational diabetes mellitus: A prospective nested case-control study among Chinese women. *Diabetes Research and Clinical Practice*, *191*, 110039. https://doi.org/10.1016/J.DIABRES.2022.110039
42. Ylli, D., Sidhu, S., Parikh, T., & Burman, K. D. (2022). Endocrine Changes in Obesity. *Perioperative Anesthetic Care of the Obese Patient*, 41–49. https://doi.org/10.3109/9781420095319-7