A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF ÇANKIRI KARATEKİN UNIVERSITY

CORRELATION BETWEEN THE LEPTIN WITH INSULIN HORMONE AS A MARKER OF DEVELOPMENTS TYPE 1 AND 2 DIABETES MELLITUS

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

BY

HAJIR ADNAN DAHHAM MAAMER

ÇANKIRI

2022

CORRELATION BETWEEN THE LEPTIN WITH INSULIN HORMONE AS A MARKER OF DEVELOPMENTS TYPE 1 AND 2 DIABETES MELLITUS

By Hajir Adnan Dahham MAAMER

December 2022

We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science

Advisor : Assoc. Prof. Dr. Melike BİLGİ KAMAÇ

Examining Committee Members:

Chairman : Assoc. Prof. Dr. Melike BİLGİ KAMAÇ
Chemistry
Çankırı Karatekin University

Member : Asst. Prof. Dr. Burcu ÖZCAN
Bioengineering
Çanakkale Onsekiz Mart University

Member : Asst. Prof. Dr. Muhammed ALTUN
Chemistry
Çankırı Karatekin University

Approved for the Graduate School of Natural and Applied Sciences

Prof. Dr. İbrahim ÇİFTÇİ
Director of Graduate School

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Hajir Adnan Dahham MAAMER

ABSTRACT

CORRELATION BETWEEN THE LEPTIN WITH INSULIN HORMONE AS A MARKER OF DEVELOPMENTS TYPE 1 AND 2 DIABETES MELLITUS

Hajir Adnan Dahham MAAMER

Master of Science in Chemistry

Advisor: Assoc. Prof. Dr. Melike BİLGİ KAMAÇ

December 2022

In this thesis, the relationship between leptin and insulin was investigated in women with type 1 diabetes (T1DM) and women with type 2 diabetes (T2DM). Fifty women with each diabetic disease were enrolled in the study and controlled with two groups of healthy women; each group controlled the corresponding patient's group that match the age. Leptin was significantly increased in the serum of women with T1DM, and women with T2DM compared to the corresponding control. Additionally, insulin was reduced in women with T1DM, but increased in women with T2DM. Glucose and glycated hemoglobin levels were increased in both groups of patients. Ghrelin was reduced in women with T1DM, and women with T2DM, while lipid profile was altered in women with T2DM disease. Leptin was not associate with insulin in women with T1DM, but it was negatively correlated with insulin in women with T2DM disease. In conclusion, leptin and ghrelin play an important role in the pathophysiology of T1DM and T2DM diseases.

2023, 69 pages

Keywords: Leptin, T1DM, Insulin, Lipid profile, HbA1c, T2DM, Ghrelin

ÖZET

LEPTİN İLE İNSÜLİN HORMONU ARASINDAKİ GELİŞMELERDE BİR İŞARET OLARAK TİP 1 VE 2 DİYABET MELLİTUS ARASINDAKİ İLİŞKİ

Hajir Adnan Dahham MAAMER
Kimya, Yüksek Lisans
Tez Danışmanı: Doç. Dr. Melike BİLGİ KAMAÇ
Aralık 2022

Bu tez çalışmasında, tip 1 diyabetli (T1DM) kadınlarda ve tip 2 diyabetli (T2DM) kadınlarda leptin ve insülin arasındaki ilişki araştırılmıştır. Her diyabet hastalığından elli kadın çalışmaya alındı ve iki grup sağlıklı kadınla kontrol edildi; her grup, yaşla eşleşen ilgili hasta grubunu kontrol etti. Leptin, karşılık gelen kontrole kıyasla T1DM'li kadınların ve T2DM'li kadınların serumunda önemli ölçüde artmıştır. Ek olarak, insülin T1DM'li kadınlarda azalmış, ancak T2DM'li kadınlarda artmıştır. Her iki hasta grubunda da glukoz ve glikolize hemoglobin seviyeleri yükselmiştir. Ghrelin, T1DM'li kadınlarda ve T2DM'li kadınlarda azalırken, T2DM hastalığı olan kadınlarda lipid profili değişmiştir. Leptinin, T1DM'li kadınlarda insülin ile ilişkili olmadığı, ancak T2DM hastalığı olan kadınlarda insülin ile negatif ilişkili olduğu görülmüştür. Sonuç olarak, leptin ve ghrelin, T1DM ve T2DM hastalıklarının patofizyolojisinde önemli rol oynamaktadır.

2023, 69 sayfa

Anahtar Kelimeler: Leptin, T1DM, İnsülin, Lipid profili, HbA1c, T2DM, Ghrelin

PREFACE AND ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Assoc. Prof. Dr. Melike BİLGİ KAMAÇ, for her patience, guidance and understanding.

Hajir Adnan Dahham MAAMER
Çankırı-2022

CONTENTS

LIST OF SYMBOLS

%	Percent
±	Plus-minus
°C	Degrees Celsius
µL	Microliter
dL	Deciliter
g	Gram
kg	kilogram
L	Liter
m^2	Square-meters
mg	Milligram
mIU	Milli international unit
mL	Milliliters
ng	Nanogram

LIST OF ABBREVIATIONS

ADA	American diabetes association
CRP	C-reactive protein
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
FSH	Follicle-stimulating hormone
GDM	Gestational diabetes mellitus
GLUT2	Glucose transporter 2
HbA1c	Hemoglobin a1c
HDL-C	High-density lipoprotein cholesterol
IGF	Insulin-like growth factor
ILPs	Insulin-like peptides
INSR	Insulin receptor signaling regulation
IR	Insulin resistance
LDL-C	Low-density lipoprotein cholesterol
LEP	Leptin
LH	Luteinizing hormone
MAPK	Mitogen-activated protein kinase
PVD	Peripheral vascular disease
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T-Chol	Total cholesterol
TG	Triglycerides

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1. INTRODUCTION

Diabetes mellitus, a worldwide disease that affects 463 million individuals, is today regarded as one of the most significant non-communicable public health concerns facing the globe in the modern period (Sciberras *et al.* 2020). Diabetes exacts a significant toll on morbidity and mortality due to its status as the primary cause of amputation, blindness, and CRD as well as a major contributor to myocardial infarction (Ml), stroke, heart failure, and (PVD) (Seidu *et al.* 2021). While type 2 diabetes (also known as T2DM) accounts for around 90–95 percent of the burden associated with diabetes, T1D (also known as T1DM and mainly affecting youngsters). Insulin deficit is the underlying cause of type 1 diabetes. This shortage is often brought on by autoimmune processes in genetically vulnerable individuals. The etiology of both types of diabetes as well as the consequences of diabetes entail the activation of oxidative stress pathways and pro-inflammatory (Brownlee 2005). Undiagnosed diabetes affects over half of the world's 463 million individuals with the condition1; in the United States, this equates to around 7.3 million persons out of a total population of 34 million who are afflicted by diabetes (Jung *et al.* 2021). Regrettably, patients with diabetes who have not yet been identified are still at danger of acquiring diabetic complications (Eades *et al.* 2015).

Hyperinsulinemia and insulin resistance come before the formation of hyperglycemia. Hyperglycemia only occurs when beta cells are unable to the adequately adjust for insulin resistance in the periphery. During the process of developing type 2 diabetes, a wide variety of variables, including free fatty acids, hyperglycemia, and cytokines have been proposed as potential mediators of cell decompensation. Although it is well established that insulin signaling is necessary for the development and function of β-cell (Kitamura *et al.* 2002). Insulin has been shown to have such long term effects on the beta cells in research conducted by groups of research (Guillen *et al.* 2008).

Leptin, a polypeptide protein of 16 kDa secreted by adipocytes, is important for regulating body weight since it aids with energy expenditure. In contrast to obesity, which promotes a variety of cellular processes that impair leptin signaling mechanisms and increase the

likelihood of weight gain brought on by hereditary and environmental factors, leptin plays a critical role in controlling metabolism and hunger (Myers *et al.* 2010). Leptin typically lowers body weight, and elevated blood leptin levels with obesity are a sign of "leptin resistance." Leptin levels that are lower imply a decrease in appetite. Although leptin concentration is increased in obese individuals, leptin levels also differ among obese individuals, suggesting that mechanisms other than fatty tissues may be involved in the regulation of leptin production and secretion (Spiegelman and Flier 2001).

Due to leptin's possible function in appetite regulation and ability to reverse DM by increasing glucose tolerance, leptin may be a promising and advantageous alternative modality that may be taken into consideration with the help of clinical studies for its safety and effectiveness (Spiegelman and Flier 2001).

The aim of study: investigate Correlation between the Leptin with insulin hormone as a Marker of developments type 1 and 2 Diabetes Mellitus and compare them with healthy controls and use these Correlation between the Leptin with insulin hormone as an indicator of developments type 1 and 2 Diabetes Mellitus.

2. LITERATURE REVIEW

2.1 Diabetes Mellitus

Chronic hyperglycemia is the primary symptom of all metabolic illnesses collectively referred to as diabetes mellitus. Either disrupted insulin secretion, disturbed insulin effect, or often both, are the causes (Schleicher *et al.* 2022).

Additionally, one kind of "lean diabetes" is understood to represent a condition in which basic flaws in insulin production, brought on by dysfunctional pancreatic beta-cells, are what ultimately cause diabetes to develop (George *et al.* 2015). As of 2014, 9.3% of Americans were said to have diabetes (29.1 million people). In the US, there is a 40% lifetime chance of acquiring diabetes (Standars of American Diabetes Association 2015). It is projected that 86.1 million individuals in the United States have prediabetes in addition to those who already have it (Standars of American Diabetes Association 2015). Diabetes is a primary source of the complications that affect almost every bodily tissue significant in terms of cardiovascular mortality, blindness, renal failure, and amputations. The early onset of significant problems and a more aggressive form of type 2 diabetes have also been associated to type 2 diabetes early diagnosis in adolescents and young adults (up to age 40 years) (Lascar *et al.* 2018). These sobering numbers highlight the critical need of identifying the underlying factors that contribute to diabetes, as well as its complications, in order to develop the most effective treatment plans.

2.1.1 Classification

The following broad categories may be used to categorize diabetes:

1. TDM1 (There may be an absolute insulin deficit as a result of the death of the beta-cells).
2. TDM2 (on account of a steadily worsening insulin secretory malfunction, which is occurring against the backdrop of insulin resistance).

3. GDM (Not overt diabetes, but diabetes discovered in the second or third trimester of pregnancy).).
4. Specific forms of diabetes brought on by unrelated conditions, such as drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or following organ transplantation), exocrine pancreas diseases (such as cystic fibrosis), and monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]).

Although not exhaustive, this section discusses the most prevalent types of diabetes. Consult the American Diabetes Association (ADA) policy statement for further details "Diagnosis and Classification of Diabetes Mellitus" (ADA 2014).

The conditions existing at the time of diagnosis are often taken into consideration when categorizing a person's type of diabetes, since not all people with diabetes can be easily categorized. A patient's type 1 or type 2 diabetes, for instance, cannot always be determined. For both kinds of diabetes, the clinical picture and disease development might differ greatly.

Both types of diabetes affect both cohorts, contradicting the conventional wisdom that type 2 diabetes exclusively affects adults and type 1 diabetes only affects children. Diabetes mellitus with ketoacidosis may sometimes be present in type 2 diabetics (DKA). The classic symptoms of polyuria/polydipsia and, sometimes, DKA are how type 1 diabetes in children commonly manifests. The signs and symptoms of type 1 diabetes in adults may differ from those in children and may not appear at all. Adults, teenagers, and children may all have trouble getting a diagnosis, but as time goes on, the accurate diagnosis will become more clear (Nowicka *et al.* 2011).

2.2 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM), commonly known as hyperglycemia in pregnancy, is the term used to describe hyperglycemia that is first noticed during pregnancy. The

second and third trimesters of pregnancy are when GDM often strikes, while it may happen at any moment over the course of the pregnancy. 7% of all pregnancies are complicated by GDM, according to the (ADA). The risk of type 2 diabetes mellitus emerging in the future is higher among women with GDM and their kids (ADA 2014).

Preeclampsia, hypertension, and hydramnios are all conditions that may make GDM more difficult to manage and increase the need for surgical procedures. Congenital abnormalities or macrosomia, or an increase in size or weight, may occur in the fetus. The respiratory distress syndrome and consequent childhood and teenage obesity may develop in such babies even after birth. GDM is more likely to occur in those who are older, obese, or who gain too much weight during pregnancy. Other risk factors include having had a stillbirth or had prior children with congenital defects (Lawrence *et al.* 2021).

2.3 Type 1 Diabetes

Diabetic autoimmune disease. Only 5–10% of people with diabetes have this kind of diabetes, which was formerly referred to as insulin-dependent diabetes or juvenile-onset diabetes. It is brought on by an autoimmune reaction that damages the pancreatic beta cells on a cellular level. Islet cell autoantibodies, insulin autoantibodies, GAD (GAD65) autoantibodies, and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β are examples of markers for immunological destruction of the β-cell. When fasting hyperglycemia is first identified, 85–90% of people have one and typically more of these autoantibodies. The DQA and DQB genes are linked to the illness, which also has significant HLA linkages, and the DRB genes have an impact on it. Both predisposing and protecting HLA-DR/DQ alleles exist (ADA 2013).

When a person has this kind of diabetes, the pace of β-cell death varies quite a little, being rapid in some people (often babies and children) and gradual in others (mainly adults). Ketoacidosis may be the initial symptom of the illness in some people, especially children and teenagers. Others have mild fasting hyperglycemia that, when triggered by an illness or another stressor, may quickly progress to severe hyperglycemia and/or ketoacidosis. Others, especially adults, could still have some -cell function, which would keep them

from going into ketosis for a long time. However, over time, they would need insulin to survive, which would put them in danger of going into ketosis. As seen by the low or undetectable levels of plasma C-peptide at this latter stage of the illness, there is little to no insulin production. Immune-mediated diabetes may strike anybody, even in the eighth and ninth decades of life. It often strikes children and adolescents (Robertson 2018).

There are several genetic predispositions for the autoimmune destruction of beta-cells, and it is also influenced by poorly understood environmental influences. The existence of obesity is not inconsistent with the diagnosis, despite the fact that people with this form of diabetes are seldom obese when they first appear. These people are also predisposed to various autoimmune diseases such Graves' disease, autoimmune hepatitis, Hashimoto's thyroiditis, celiac sprue, Addison's disease, vitiligo, myasthenia gravis, and pernicious anemia, diabetes idiopathic**.** There are certain types of type 1 diabetes whose causes are unknown. Some of these individuals lack autoimmune signs yet have persistent insulinopenia and a propensity for ketoacidosis. The majority of people with T1D who fit this description which is a small percentage have African or Asian heritage. This kind of diabetes causes episodic ketoacidosis, and those who have it display varied degrees of insulin insufficiency in between episodes. Although there is no scientific proof of β-cell autoimmunity and this kind of diabetes is not HLA related, it is highly inherited. It may or may not always be necessary for afflicted people to get insulin replacement medication (American Diabetes Association 2014).

2.3.1 Pathophysiology of type 1 diabetes

The majority of studies on the pathophysiology of type 1 diabetes start by noting that the condition is brought on by an autoimmune attack on cells in the pancreas that secrete insulin. This finding is supported by the discovery of a persistent inflammatory infiltration that damages pancreatic islets with the start of type 1 diabetes symptoms (In't veld 2011). Another myth is that the pancreas is bereft of insulin-producing cells in individuals with chronic illness, and the remaining beta cells are incapable of regenerating. These two theories of the pathophysiology of type 1 diabetes have generated disagreement (Gregg *et al.* 2012). Analysis of pancreatic samples, serum, and peripheral

blood lymphocytes acquired from type 1 diabetes patients has contributed significantly to our understanding of the etiology of the disease (Roep and Peakman 2011). Studies on these components lead to the conclusion that the pathophysiology of type 1 diabetes is caused by a number of functional problems in the bone marrow, thymus, immune system, and β-cell (Figure 2.1).

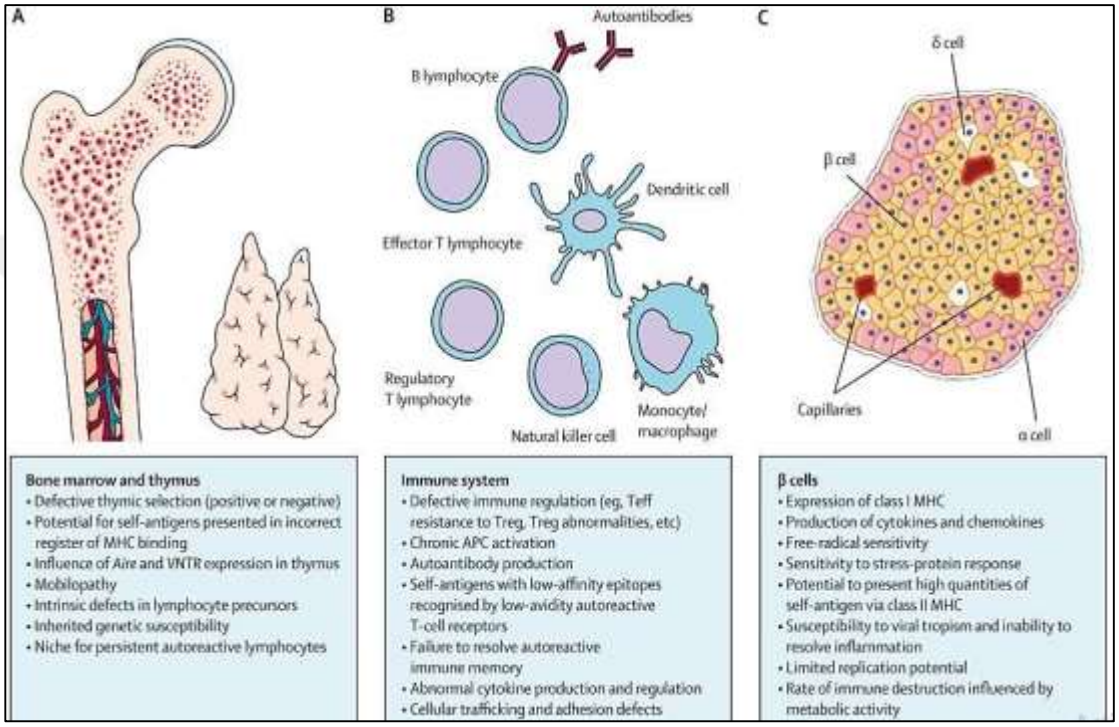

Figure 2.1 Physiological contributions to the pathogenic processes that underlie type 1 diabetes (Atkinson *et al.* 2014)

2.4 Type 2 Diabetes

Type 2 Diabetes Mellitus (T2DM), one of the most common metabolic illnesses, is brought on by the interaction of two main factors: reduced insulin secretion by pancreatic beta-cells and impaired insulin sensitivity in target tissues. For insulin to precisely meet metabolic demand, the molecular mechanisms involved in its synthesis, release, and response in tissues must all be under appropriate control. The pathogenesis of T2DM may thus be caused by flaws in any of the systems at play, which might result in a metabolic imbalance. This study examines the main features of T2DM as well as the pathways and

molecular processes involved in insulin metabolism and the connections between T2DM and cardiovascular disease (Essaouiba *et al.* 2020).

2.4.1 Pathophysiology of type 2 diabetes

Insulin insensitivity is a feature of type 2 diabetes brought about by insulin resistance, reduced insulin production, and finally failing pancreatic beta cells (Olokoba *et al.* 2012). As a result, less glucose is transported into the liver, muscle cells, and fat cells. There is an increase in fat breakdown due to hyperglycemia. Decreased alpha-cell activity is a pathophysiology of type 2 diabetes, according to recent studies (Garcia-Roves 2011).

This dysfunction prevents meals from lowering the glucagon and hepatic glucose levels that rise during fasting. Low insulin levels and increasing insulin resistance result in hyperglycemia. Important gastrointestinal mediators of insulin release and, in the case of Glucagon-like peptide 1 (GLP-1) glucagon suppression, are incretins. GLP-1 is a potentially helpful treatment alternative since, despite the fact that GIP activity is decreased in people with T2DM, GLP-1 insulinotropic effects are intact. However, in vivo, Dipeptidyl-peptidase IV (DPP-IV) quickly inactivates GLP-1, much as it does with glucose-dependent insulinotropic polypeptide (GIP) (Fujioka 2007).

GLP-1 analogues with longer half-lives and DPP-IV inhibitors, which stop the breakdown of both GIP and endogenous GLP-1 have been developed as two treatment options for this issue (Fujioka 2007). In addition to having the potential to regulate fasting and postprandial glucose levels, both types of drugs have also shown promise in terms of their ability to increase beta-cell mass and function. Ongoing research is being done to determine how mitochondrial dysfunction contributes to the genesis of T2DM and the development of insulin resistance (Garcia-Roves 2011). Adipose tissue is also crucial because, according to the endocrine organ hypothesis, it may be a source of beta-cell dysfunction and insulin resistance due to the release of a number of adipocytokines, including leptin, TNF-alpha, resistin, and adiponectin (Fujioka 2007).

The majority of people with T2DM have central visceral adiposity and are obese. Adipose tissue therefore plays a significant role in the etiology of T2DM. Although the portal/visceral hypothesis is the most often utilized explanation to explain this connection and places a major emphasis on high non-esterified fatty acid concentrations, two additional ideas are developing. These two ideas serve as the foundation for future research on the relationship between type 2 diabetes risk and our obesogenic environment as well as the interaction between insulin resistance and beta-cell malfunction (Fujioka 2007).

2.4.2 Clinical implications and individualized treatment

The necessity of individualized therapy based on patient characteristics and comorbidities is emphasized in the guidelines for managing T2D released by the American Diabetes Association and the European Association for the Study of Diabetes. Treatment with (SGLT2i) or (GLP-1RA) is advised for patients with established cardiovascular disease or (CKD), but for other patients, the choice of available treatment options is concentrated on the lowering glucose, by gradually adding other medications other than metformin, and is determined by financial constraints or the severity of obesity, hyperglycemia (Mantsiou *et al.* 2020).

Because the subtypes vary clinically, adopting a course of therapy that targets the primary metabolic abnormality (such as insulin insufficiency in [SIDD] or insulin resistance in [SIRD]) may also be advantageous (Silvia *et al.* 2020).

It has long been known that insulin resistance increases the likelihood of developing diabetic kidney disease (DKD) and has been shown to do so through a variety of pathways (Mitrofanova *et al.* 2019). Even in a normoglycemic setting, podocyte-specific ablation of insulin receptor in the mice results in histological and albuminuria characteristics that mimic DKD (Welsh *et al.* 2010). The development of DKD by the SIRD subtype despite rather excellent metabolic control and low levels of HbA1c suggests that therapy of these individuals should put more of an emphasis on improving insulin sensitivity than just decreasing glucose. People with SIRD already had reduced eGFR before diagnosis, which

suggests that the pathogenic process begins before diabetes is diagnosed and that possible therapy should begin prior to the development of hyperglycemia (Ahlqvist *et al.* 2020).

It needs to be seen if the subtypes' specific differential therapy has any advantages. The (ADOPT) and record trials, which looked at three different therapies for individuals who were glutamic acid decarboxylase autoantibody-negative (GADA-negative), provided some preliminary indications of such a benefit (Dennis *et al.* 2019). While the thiazolidinedione insulin sensitizer rosiglitazone had the greatest impact on lowering HbA1c in the SIRD subtype, the insulin secretagogue sulfonylurea had the best results with the age-related mild age-related diabetes (MARD) individuals (Dennis *et al.* 2019). Despite having significantly different risks of complications, MARD and SIRD patients in the All New Diabetics in Scania (ANDIS) cohort received identical therapy (Ahlqvist *et al.* 2018b). Thiazolidinediones have been shown to be successful in lowering albuminuria, even while meeting the same HbA1c objectives, despite the fact that the impact on eGFR was not examined in the adopt and record studies (Schernthaner 2004). Given that insulin resistance seems to play a significant role in development of the (DKD), this impact may be much more pronounced in the (SIRD) patients.

Although these findings are promising, clinical studies that link the therapeutic benefits of additional drugs to specific diabetes subgroups are still required. Given their potential to stop side effects such chronic kidney disease (CKD) and fatty liver, the effectiveness of GLP-1 agonists and insulin in insulin sensitizers in SIRD has to be examined. SAID has a special function among the insulin-deficient populations since it may be detected by the measurement of autoantibodies and is therefore amenable to early insulin treatment targeting.

2.4.3 Relation between diet and type 2 DM

Indians, as indicated earlier, put out the idea that nutrition may have a part in the genesis of T2DM. They did this after seeing that the illness was virtually exclusively seen in wealthy individuals who ate large quantities of bread, sugar, and oil. Due to famines and food shortages in the affected nations, including Germany and other European nations,

the death rates for diabetes were shown to have decreased during the First and Second World Wars. From 23.1/100,000 in 1914 to 10.9 in 1919, Berlin's diabetes mortality rate decreased. Other nations, including Japan and North American nations, where there was no food crisis at the same time, however, did not see a shift in the death rate for diabetes (Sami *et al.* 2017). However, only a few studies have revealed a clear link between T2DM and a high carbohydrate and fat diet. High sugar consumption and the development of the (T2DM) have been linked favorably in several studies. Ludwig spent 19 months observing more than 500 students from various ethnic backgrounds in research. It was determined that the likelihood of obesity increased with each additional serving of carbonated beverages consumed after taking into consideration a number of variables, including dietary, demographic, anthropometric, and lifestyle decisions (Ludwig *et al.* 2001).

Due to the massive quantities of high fructose corn syrup used in the manufacture of soft drinks, which increases blood glucose levels and Body Mass Index (BMI) to hazardous levels, there has recently been evidence linking use of soft drinks with obesity and diabetes. Amin *et al.* also claimed that the glycated compounds included in diet soft drinks significantly increase insulin resistance. Obesity and food consumption have a close relationship, and this relationship is influenced by dietary type and quantity as well as amount of food consumed (Amin *et al.* 2008). Increased risk of insulin resistance and T2D is associated with a high diet of red meat, sweets, and fried meals (Panagiotakos *et al.* 2005). On the other hand, there was a negative connection between vegetable consumption and T2DM. Fruits and vegetables are rich in nutrients, fiber, and antioxidants, which are believed to serve as a barrier against disease and may stop the onset of T2DM (Villegas *et al.* 2008). A study found that eating more white rice was linked with higher risk of developing T2DM in women’s of Japane (Nanri *et al.* 2010). The general people must immediately change their lifestyles, and knowledge of good eating habits must grow across all demographics.

2.5 Risk Factors for Diabetes

Because DM is now more common, the severity of the public health issue has become worse globally. Several risk factors contribute to the disease's actual start. The main risk factors for DM and prediabetes are environment, genetics, loss of the very first phase of insulin release, loss of physical activity, sedentary lifestyle, use of alcohol, smoking, dyslipidemia, decreased ß-cell sensitivity, hyperinsulinemia, and increased glucagon activity (Lee *et al.* 2012). These elements seem to have a big impact on how the illness progresses due to insulin resistance or insulin non-functionality. According to WHO (2011), T2DM affects 90% of patients, mostly due to increased body weight. A frequent risk factor for glucose sensitivity and insulin resistance, which together advance to prediabetes and subsequently T2DM. it is believed that a diet with a high glycemic index (GI) but low fiber content contributes to the development of diabetes (Li *et al.* 2015).

There is evidence that one significant connection between insulin resistance and T2DM is free fatty acids. Soft drinks may promote raise BMI and obesity which can cause T2DM. The most harmful aspect of these beverages is the high sugar load and subsequent the metabolic effects on liver. The development of T2DM is caused by the dysregulation of adipokines and resistins, which are increased in bulk when a person is overweight (Sears and Perry 2015). Numerous research has looked at the connection between hyperuricemia and the development of T2DM. The β-cell function is activated from its compensatory state in individuals with hyperuricemia and insulin resistance (Jia *et al.* 2006). In a different research, C-peptide levels were observed to rise in individuals with obesity and T2DM when four study groups were compared. It seems that the behavior of uric acid and β cell function are tightly connected. It was discovered in a subsequent investigation that elevated blood uric acid was linked to a greater risk of T2DM independently of dyslipidemia, and obesity. However, uric acid has been shown to be a mediator of endothelial dysfunction and systemic inflammation and to contribute to cytokine release (Lytvyn *et al.* 2015).

A proinflammatory response and negative effects on endothelial function, both of which are known to be connected to the start of T2DM, may potentially result from this.

Numerous research has shown a link between high blood uric acid levels and diabetes (Kodama *et al.* 2009).

2.6 Insulin

Insulin-like peptides have been discovered in all mammals. ILPs invertebrate offer mitogenic signaling input, but their influence on the metabolic functions and fuel choice are less prominent. Animals have developed specialized functions for the peptide hormones linked to insulin, insulin-like growth factor 2 (IGF-2) and, insulin-like growth factor 1 (IGF-1) by taking advantage of gene duplication events during evolutionary time (Jin-Chan and Steiner 2000). In contrast to insulin, which largely regulates metabolic fluxes, IGF-1 and IGF-2 stimulate cell proliferation and differentiation in animals (Dupont *et al.* 2001). The substantial similarity of the insulin and IGF-1 receptors, which form hybrid heterodimers in a variety of cell types and share several downstream effectors, however, draws attention to the fuzziness of these functional differences (Bedinger and Adams 2015). The well-established link between hyperinsulinemia and a number of malignancies is most likely also influenced by the similar signaling roles that insulin and IGF-1 play (Perseghin *et al.* 2012).

2.6.1 Insulin synthesis, processing, and packaging in pancreatic β-cells

On chromosome 11, the human INS gene is the only one that produces insulin. Upstream enhancer sites that bind significant transcription factors including MafA, (PDX1), and NeuroD1, in major part control the transcription of this gene, as well as a number of coregulators (Artner and Stein 2008). In the insulin-producing pancreatic beta-cells, where they are required for insulin gene expression, they are crucial for the regulation of INS transcription in response to autocrine insulin signaling and glucose (Andrali *et al.* 2008). Given that they are responsible for controlling the expression of insulin and a variety of other components of the β-cell secretory pathway, their coregulators, and transcription factors are crucial defining factors in the maintenance and the creation of β-cell identity (Gao *et al.* 2014).

The signal peptidase in the RER cleaves the signal sequence of insulin, which is first translated as preproinsulin, and then converts to proinsulin. The semi-helical A domain and the helical B domain are connected by three disulfide bonds, folding and stabilizing proinsulin into its three-dimensional (3D) proinsulin form. After passing through the Golgi apparatus, where it is broken down by the prohormone convertases PC1/3 and PC2, the correctly folded proinsulin is sorted into the secretory granules that are continually growing. The final product is mature insulin, which is made up of A- and B-peptide chains connected (Tokarz *et al.* 2018).

2.6.2 Insulin resistance

When an organism's cells, tissues, or bodies cannot appropriately react to normal amounts of insulin, the condition is known as insulin resistance. As a result, insulin's ability to maintain lipid and glucose homeostasis is compromised. Insulin's failure to maintain normoglycemia results in compensatory hyperinsulinemia, which boosts β-cells' capacity to secrete insulin. Pancreatic beta-cells get exhausted and undergo apoptosis when insulin is secreted over an extended length of time (Mezza *et al.* 2019). Additionally, insulin resistance encourages gluconeogenesis in the liver, interferes with glucose absorption in muscles, and triggers lipolysis in adipose tissues (Fujimoto 2000).

2.6.3 Role of IR in the development of metabolic dysfunction

Glycogen production, the capacity to control lipid oxidation, and the absorption and oxidation of glucose are all reduced as a result of insulin resistance (IR) (Ormazabal *et al.* 2018). Metabolic syndrome is a collection of cardiovascular and metabolic abnormalities that are caused by the disruption of the Phosphoinositide 3-kinase (PI3-K) insulin pathway, which is a crucial factor in the development of the metabolic dysfunction (including: hypertension, dyslipidemia and dysglycemia) (Frisardi *et al.* 2010).

Hypertension: IR induces compensatory hyperinsulinemia, which may raise blood pressure via a number of different processes. The sympathetic nervous system is

activated, resistant blood vessels become larger, and renal sodium absorption of sodium is increased (Cwynar *et al.* 2005). In addition to altering the shape of vasculature and the impairing vasodilation within the skeletal muscle, the development of hypertension may also lead to a worsening of IR due to decreased glucose and insulin supply to the skeletal muscle cells. It's interesting to note, however, that research on animal models of hypertension suggests that IR really occurs before hypertension manifests, supporting IR's causative involvement in the development of hypertension. Additionally, variations in autonomic control appear to alter insulin sensitivity, according to research done on healthy human volunteers. Thus, due to its impact on vasoconstriction, autonomic imbalance may cause both IR and hypertension (Frontoni *et al.* 2005).

Dyslipidaemia: IR causes a greater hepatic flow of dietary fats and resistance to insulin's antilipolytic actions in adipose tissue, which both contribute to dyslipidaemia. These changes in lipid metabolism are characterized by dyslipidaemia and the classic proatherogenic lipid trio of tiny and dense LDL, high plasma triglycerides, and low plasma HDL (Sparks *et al.* 2012). Furthermore, these IR-induced lipid profile deviations may be a factor in the endothelium's inflammatory reactions.

2.6.4 Insulin receptor signaling regulation overview

INSR plays a significant role in several fundamental biological processes, that including as energy metabolism and proliferation. In metabolic diseases like diabetes, INSR activities are often dysregulated. Understanding the thorough control of INSR, also its downstream the signaling events is crucial given the abnormalities of the INSR function in the etiology of the diabetes. It has been demonstrated that the essential trafficking and control of INSR, which is a member of (RTK) family, have been established. On the other hand, there is a paucity of information about the molecular mechanisms that are driving these actions. Endocytosis triggered by ligands binding to receptor tyrosine kinases (RTKs) is a process that is often considered to be a way of signal termination that regulates the magnitude and length of receptor activity. The extended insulin signaling in cells lacking INSR endocytosis (Boothe *et al.* 2016) lend credence to this idea. The

widespread consensus is that insulin resistance, a significant contributor to metabolic diseases, is a post-receptor signaling malfunction where INSR activities are unaffected.

2.7 Leptin and Leptin Receptors

The obese (ob) gene's functional offspring is the endocrine hormone leptin. Leptin is primarily produced in white adipose tissue, and once released, it has a direct correlation with body fat levels in the blood (Considine *et al.* 1996). Through a transport system that is saturable and very sensitive to adrenaline and triglycerides, peripherally generated leptin easily enters the brain (Banks *et al.* 2004). Leptin's central effects are mostly mediated by hypothalamic neuronal circuits, with the arcuate nucleus playing a significant role in this hormone's capacity to regulate energy levels. The hippocampus and cerebral cortex are only two parts of the brain that produce leptin receptors at high density, demonstrating that leptin's neuronal activities go beyond the hypothalamus (Könner *et al.* 2009).

There are six different isoforms of the leptin receptor, ObRa-f, and diabetes (db) gene that produce leptin receptors. Except for ObRe, all of the isoforms have comparable external domains, are expressed in the plasma membrane, and have different intracellular domain lengths. The long isoform of the leptin receptor, on the other hand, contains a longer (302 residues) intracellular domain, allowing this isoform to activate all the leptin receptors signaling pathways. In contrast, only a small subset of the signaling molecules directed by the Ob-Rb is activated by short isoforms, which have a restricted ability to signal. Despite lacking a membrane-spanning domain, ObRe also is a new leptin receptor isoform that binds leptin with ease. Leptin binding to ObRe is thus believed to facilitate the plasma transport of ObRe (Presle *et al.* 2007).

Leptin receptors and other class I cytokine receptors, which are a set of the receptors that also including interferon receptors, have a high degree of similarity with one another. Janus tyrosine kinase 2 (JAK2) is activated by leptin binding to ObR, which encourages JAK2 phosphorylation. As a result, some intracellularly situated tyrosine residues may be phosphorylated. The activation of several signaling pathways by ObRs is made possible

by this series of events. Neuronal ObRs primarily stimulate the signaling molecules phosphoinositide-3 kinase (PI 3-kinase), mitogen-activated protein kinase, and the signal activator and transduction of transcription (STAT) transcription factors (Farooqi and O'Rahilly 2014).

2.7.1 Leptin and puberty

The beginning of puberty, which is a "metabolically gated" stage in a person's life, is significantly influenced by nutritional condition (Sanchez-Garrido *et al.* 2013). Similarly, leptin is widely known as a possible endocrine agent that makes a connection between energy reserves (adiposity) and the advancement of various puberty events as a vitally decisive amount of body fat is required to accomplish sexual maturity. Leptin was first assumed to indicate energy storage, which would then act as a catalyst for the development of puberty. During the pre-pubertal years of both girls and boys, leptin concentration has been seen to increase gradually with age and total body fat (Apter 2003), followed by an initial rise in (FSH), (LH), and subsequently sex steroids. Leptin and body fat mass both continue to rise throughout puberty in females, perhaps as a result of estrogen's stimulatory actions, but they fall in boys, with the possible exception of a rising body mass index, potentially as a result of testosterone's inhibitory effects. According to reports, leptin has a permissive function in pubertal development. However, it was shown that exogenous leptin alone was unable to cause early puberty in the individuals with congenital leptin insufficiency (Farooqi *et al.* 2002). There may be more than one hyperleptinemia symptom involved in the early onset of puberty seen in obese children. even when the hyperleptinemia manifests with leptin resistance or tolerance. It has been discovered that previous leptin injection, which did not hasten the start of puberty, is connected to lower food intake. Leptin administration, which results in a negative energy balance, may clearly avoid pubertal growth delays (Cheung *et al.* 2001).

2.7.2 Pathophysiology and clinical relevance of leptin

Increased vulnerability to infections, autoimmune diseases, malnutrition, and inflammatory reactions are all linked to leptin deficit or resistance, as well as dysregulated cytokine production (Figure 2.2) (Maurya *et al.* 2018).

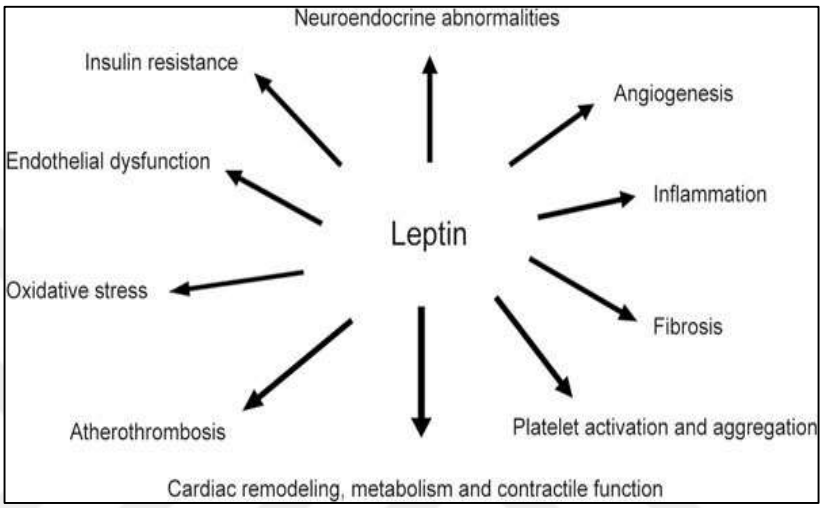

Figure 2.2 Pathophysiological mechanisms affected by leptin (Katsiki *et al.* 2018)

Hyperinsulinemia, hepatic steatosis, dyslipidemia, hypogonadotropic hypogonadism, intense hyperphagia, continual food seeking, severe obesity, decreased satiety, intensive hyperphagia, hypogonadotropic hypogonadism, and complete leptin insufficiency are the clinical manifestations of hypoleptinemia (Funcke *et al.* 2014). These phenotypes show the range of functions that leptin performs inside the body, many of which are currently being actively researched. Congenital leptin deficits, which are caused by mutations in the LR or LEP genes, are congenital types of hypoleptinemia (CLD). Acquired hypoleptinemias, which are often brought on by illnesses that lower body weight, have some of these similar characteristics. Acquired conditions include hypothalamic amenorrhea and lipodystrophic disorders (Paz-Filho 2016).

Hyperleptinemia: It is characterized by leptin resistance, notable resistance to the anorectic and body weight-decreasing effects of leptin. Common obesity is characterized by hyperleptinemia and leptin resistance. Leptin blood levels and adipocyte LEP mRNA

content was shown to be directly correlated with body fat percentage in obese persons, as opposed to normal-weight individuals, providing evidence for this link. Adipocyte LEP mRNA content and leptin blood levels both decrease with weight loss. Leptin deficiencies seem to be a factor in the resistance mechanism (Knight *et al.* 2010).

Non-alcoholic fatty liver disease, neurodegenerative illnesses, the depression, and food addiction are other conditions connected to hyperleptinemia (Peters *et al.* 2018).

Therapeutics: The treatment of both the hypoleptinemia and the hyperleptinemia-related syndrome using recombinant versions of leptin is being studied. Leptin replacement was first investigated to treat obesity; however, it has only shown effective in leptin-deficient circumstances, with minimal success in usually obese people with increased leptin levels. Congenital or acquired widespread lipodystrophy may be treated with FDA permission (non-HIV-related). However, these disorders are not currently recognized as indications for the use of recombinant leptin as a therapeutic, despite research showing that leptin replacement is effective in rectifying several abnormalities found in the aforementioned syndromes (Paz-Filho *et al.* 2015).

2.7.3 Leptin and glucose metabolism

In addition to its impact on one's body weight and the amount of food consumed, leptin has a fundamental function in the control of glucose homeostasis via activities in the CNS and peripheral tissues (Frühbeck and Salvador 2000). Specialized subsets of hypothalamic neurons in the central nervous system (CNS) react to variations in extracellular glucose concentrations. By activating ATP-sensitive K^+ channels, leptin hyperpolarizes them and reduces their activity. A significant feeding-independent regulator of leptin signaling, glucose homeostasis, particularly in the hypothalamic ARC, helps to improve hyperinsulinemia and normalize blood glucose levels. As a result, it has been suggested that the hypothalamus is a crucial location for the integration and control of energy homeostasis (Coppari *et al.* 2005). Skeletal muscle is regarded as the primary location of insulin- and exercise-stimulated glucose disposal at the peripheral level (Sainz *et al.* 2009). The negative GLUT4 traffic regulators TBC1D1 and TBC1D4 are expressed

and active less often when leptin is present, which improves intracellular GLUT4 transport. Leptin has complicated effects on the intrahepatic partitioning of metabolic fluxes, and on the expression of important metabolic enzymes in the liver, which together increase insulin sensitivity (D'souza *et al.* 2017). Leptin treatment reduces the effects of insulin on the hepatic glucose production. Gluconeogenesis is boosted by leptin, which also inhibits some of insulin's actions. It is necessary to properly understand the intricate regulatory impact of leptin on the liver, however. Leptin decreases both the basal and insulin production induced by glucose in pancreatic beta-cells, according to compelling in vivo and in vitro data. Leptin also inhibits pancreatic-cell function in obese people and animals, as well as preproinsulin mRNA expression. Leptin also lessens insulin sensitivity as well as insulin-stimulated glucose incorporation and uptake into lipids in the rodent adipocytes via a variety of pathways (Tudur *et al.* 2009).

2.7.4 Leptin and T2DM

Insulin resistance and the development of T2DM are linked to elevated leptin levels (Blüher 2014). The prevalence of microvascular problems and cardiac autonomic dysfunction in T2DM has also been described, as well as a connection between elevated leptin concentrations and higher cardiovascular (CV) risk. In this situation, leptin levels were associated with carotid atherosclerosis (as determined by cIMT) in T2DM patients, as well as the occurrence and severity of silent myocardial infarction (MI). Additionally, T2DM individuals with higher leptin levels are more likely to have endothelial dysfunction, obesity, hypertension, metabolic syndrome (MetS) (Morioka *et al.* 2014). Notably, both T2DM patients and healthy people have evidence that leptin levels drop after an oral fat-tolerance meal. Additionally, linked to the existence of T2DM are certain leptin gene polymorphisms (Zhang *et al.* 2018, Yang *et al.* 2016). In individuals with lipodystrophy, leptin replacement treatment has been shown to reduce liver and muscle insulin resistance (Perry *et al.* 2016).

Only sitagliptin, a Inhibition of dipeptidyl peptidase 4 (DPP-4) inhibitor, has been found to lower blood leptin levels in trials on both humans and animals. This is the only DPP-4 inhibitor for which data are available. According to (Farooq *et al.* 2017) metformin may

also increase the expression of leptin receptors in mouse livers and reduce leptin concentrations in T2DM patients' blood (a condition known as type 2 diabetes). With the use of metformin, a reported increase in leptin hypothalamic sensitivity was seen. Metformin also decreased the expression of matrix metalloproteinase-2, smooth muscle cell proliferation, and leptin-related reactive oxygen species. A noteworthy finding from a meta-analysis was that metformin was shown to lower leptin levels in women with (PCOS). Despite mixed findings, pioglitazone medication may reduce leptin levels (Miyazaki *et al.* 2008).

2.8 Ghrelin in DM

Ghrelin regulates glucose metabolism in addition to controlling food intake and energy balance. In addition, the available data point to ghrelin's potential role in metabolic syndrome. Obesity, T2DM, and other pathophysiological disorders with metabolic abnormalities have all been demonstrated to result in lower ghrelin concentrations (Wiedmer *et al.* 2007).

(UAG) and (AG), in which Ser 3 is octanoylated, are the two distinct forms of circulating ghrelin as a consequence of posttranslational changes that are made to ghrelin as a target. The potential that the UAG/AG ratio may contribute to the development of metabolic syndrome is raised by reports of a relative excess of the AG compared to UAG in cases of the insulin resistance and other disorders (Pulkkinen *et al.* 2010).

2.9 Lipid Profile and T2DM and T1DM

Diabetes-related lipid abnormalities, often known as "diabetic dyslipidemia," are frequently characterized by high (T-Chol), high (Tg), low (HDL-C), and elevated amounts of tiny dense LDL particles. Values of LDL-C may be normal or slightly elevated (Bhowmik *et al.* 2018). persons with T2DM and prediabetes often have lipid abnormalities, but the distribution of these abnormalities varies depending on the patient's ethnicity, socioeconomic status, and access to medical treatment (Joshi *et al.* 2014).

According to a newly released meta-analysis, the risk of T2DM is partially reflected by aberrant levels of the lipid markers described above. Additionally, investigations in individuals with T2DM have shown a stronger link between CAD and high Tg and low HDL-C together, as opposed to the two lipid markers evaluated independently (Lee *et al.* 2017).

Insulin increases the formation of tiny HDL particles in T1DM patients with adequate glycemic control, often leading to levels of HDL cholesterol above normal. HDL dysfunction is revealed by the finding that these high HDL cholesterol levels do not seem to provide protection against CVD, indicating that HDL cholesterol in diabetes has not developed physiologically (Schofield *et al.* 2013).

2.10 C-Reactive Protein and Diabetes Mellitus

The liver produces the pentameric (CRP) which has been known as the "golden flag for inflammation." Diabetes patients are shown to have substantial levels of hs-CRP among other inflammatory markers. The rise in serum CRP levels is correlated with hyperglycemia. One of the most sensitive indicators of systemic inflammation is CRP. The risk of future myocardial infarction, stroke, peripheral vascular disease, and cardiovascular mortality in populations who seem to be healthy has been shown to be correlated with baseline levels of CRP in several studies (Çoban and Sarı 2003).

In comparison to healthy individuals, hypertensive patients with DM showed greater levels of the circulating inflammatory marker High-sensitivity C-reactive protein (hs-CRP). This research implies that individuals with two related disorders have an elevated level of inflammation (Lima *et al.* 2007).

2.11 HbA1c and Diabetes Mellitus

When evaluating glycemic management, (HbA1c) is often employed as a marker for the three-month period prior to the measurement's average blood glucose level. The

preoperative HbA1c level has been advised by several standards to be below a certain threshold in order to improve surgical results, although the amounts vary widely. HbA1c levels should ideally be less than 7% or 6.5%, according to some criteria, whereas 8.5% or 8%-9% was preferred by others. The morbidity and mortality of the operations in patients with diabetic were not increased by elevated preoperative HbA1c levels, according to a systematic review. However, it failed to specifically address the high threshold of the preoperative HbA1c, which makes it unsuitable to support the formulation of a recommendation. Preoperative HbA1c levels and outcomes after heart surgery are yet unknown in non-diabetic individuals (Wang *et al.* 2020).

3. MATERIALS AND METHODS

3.1 Design of Study

In this study, a series cross-sectional studies were measured with a group comparison of clinical cases of T1DM and T2DM with the control group. Variables were measured for Age, Weight, Body Mass, Height, Leptin, Insulin, Fasting Serum Glucose, Glycated Hemoglobin, Total Cholesterol, Triglycerides, High-Density Lipoprotein-Cholesterol, Very Low-Density Lipoprotein-Cholesterol, Low-Density Lipoprotein-Cholesterol, C - reactive protein, and Ghrelin. Samples were collected from Baghdad Teaching Hospital - Baghdad, Iraq from December 2021 to April 2022

In this study included 50 women with T1DM, and 50 women with T2DM. Furthermore, the study was controlled with the two groups of control; 25 Control I, which were matched in age with T1DM women, and 25 Control II, which were matched in age with T2DM women.

3.2 Samples (Patients) Selection

Patients who met the requirements were invited to participate in the trial. Patients were fully informed of the increased risks involved in the procedure as well as the necessity of venous blood draws. Patients who agreed to the participate in study received a comprehensive clinical evaluation, and clinical information was collected using a standardized format. The patient had already requested a biochemical test at the time of the initial assessment. In accordance with the research protocol, further complementary laboratory tests were sought. A standard format was used to record each result.

3.3 Materials

3.3.1 Equipment and tools

In this researche all tools and equipment used were included, (Table 3.1, Figure 3.1, Figure 3.2 and Figure 3.3).

Table 3.1 Equipment and tools

NO	EQUIPMENT AND TOOLS	ORIGIN
1	Autoclave	Japan
2	Spectrometer	Varian/Austria
3	Deep Freeze	Germany
4	Distiller	Germany
5	Eppendorf tube (1.5mL)	China
6	1 mL pipette tips	China
7	Micropipettes (100-1000µL), (5-50µL), (20-200µL), (2-20µL)	Slamed / Germany
8	Incubator	Fisher Scient./Germany
9	EDTA tube	China
10	Water bath	GFL / Germany
11	Cobas C111	Germany
12	0.01 mL pipette tips	China
13	ELISA reader and washer	Biotech /USA

Figure 3.1 ELISA washer used

Figure 3.2 ELISA reader used in this study

Figure 3.3 Cobas C 111 used

3.3.2 Kits used

As shown in Table 3.2, in this study all kits used were included (Table 3.2).

Table 3.2 All kits are used in this study

NO	KITS USED	CAT. NO.
1	Glycated Hemoglobin	-
2	Human Ghrelin (GHRL) ELISA Kit	MBS283919
3	Fasting Serum Glucose	-
4	Rapid Insulin Test System	5825-300
5	Total Cholesterol	REF 03039773190
6	Triglycerides	REF 04657594190
7	Very Low-Density Lipoprotein	TG/5
8	Low-Density Lipoprotein-Cholesterol	REF 07005717190
9	High-Density Lipoprotein-Cholesterol	REF 07528566190
10	Human C-Reactive Protein (CRP) ELISA Kit	REF 1668-18
11	Human Leptin (LEP) ELISA Kit	MBS020274

3.4 Methods

3.4.1 Human c-reactive protein (CRP) ELISA kit

Test principle: Based on the theory of solid enzyme-linked immunosorbent assay, hsCRP ELISA is developed. 24 The antigenic determinant of the CRP molecule was specifically targeted by a single monoclonal antibody used in the testing technique. To immobilize the solid phases, this mouse monoclonal anti-CRP antibody (on micro-wells) was used. The enzyme-conjugated antibody solution (horse peroxidase) contains a goat anti-CRP antibody. CRP molecules fall between the solid phase and the enzyme-bound antibodies as a result of allowing the test sample to react with the two antibodies simultaneously. Wells were rinsed with water to get rid of the unbound antibodies after a 45 min incubation at room temperature. After addition of tetramethylbenzidine (TMB) reagent and a 20-min incubation period, a blue color developed. With the addition of 1N HCl, the color changes to yellow and color development has stopped. The color intensity of the test sample and the concentration of CRP were directly proportional to it. Spectroscopically, the absorption is measured at 450 nm.

3.4.2 Human leptin (LEP) ELISA kit

Assay Procedures:

1. Before doing the research, it was made sure that there is no problem with the device and the motherboard. Bottle/bottle labels and colored caps were checked to ensure they were consistent and error-free.
2. Before starting the test methods, the plate and all reagents and samples normally reached room temperature (18°C-25°C).
3. The board from the foil bag has been removed. The board is removable, we put the remaining strips in a foil bag with the dryer package before sealing it to prevent moisture.
4. We set up empty, standard, and sample wells.
5. We filled all the empty wells with nothing, also we added 50 µL of the standard (S1, S2, S3, S4, S5, S6) to the corresponding standard wells; We filled all sample wells with 50 µL of sample.
6. Excluding empty wells, we added 100 µL of HRP-Conjugate Reagent to each well.
7. We placed a plate-closure membrane on top of the plate and incubated it for 60 min at 37 °C.
8. We rinsed all the wells (even the empty ones) four times.
9. Filled each well with 50 µL of chromogen solution A.
10. Filled each well with 50 µL of Chromogen B solution. (Any light from Chromogen B solution removed.)
11. We mix gently, then incubate the dish at 37 °C for 15 minutes. (And direct sunlight on the panel should be avoided.
12. We filled each well with 50 liters of stopping solution.
13. We used an ELISA reader to measure the (O.D.) at 450 nm (about 5 minutes which is considered an ideal time) within 15 minutes after applying the Stop Solution,

3.5 Statistical Analyses

The statistical tools SPSS version 26.0 (SPSS-26) and Microsoft Excel 2016 were used to analyze the data. Using an ANOVA with a 95% confidence interval, mean values were compared between the control group and T1DM and T2DM patients. Utilizing the Chi-square test, percentage comparisons were made. Pearson's correlation coefficient was used to assess the association between each pair of variables in the serum of T1DM and T2DM patients (r).

4. RESULTS

4.1 Age

The age in Control I (16.16±2.34 year) and T1DM women (16.22±2.38 year), was non-significantly different (P>0.05). Moreover, the age in Control II (43.80±9.84 year), and T2DM women (41.26±10.31 year), was also non-significantly different (P>0.05). Nevertheless, the age of women with T2DM was (P<0.05) significantly higher than the age of T1DM women (Figure 4.1).

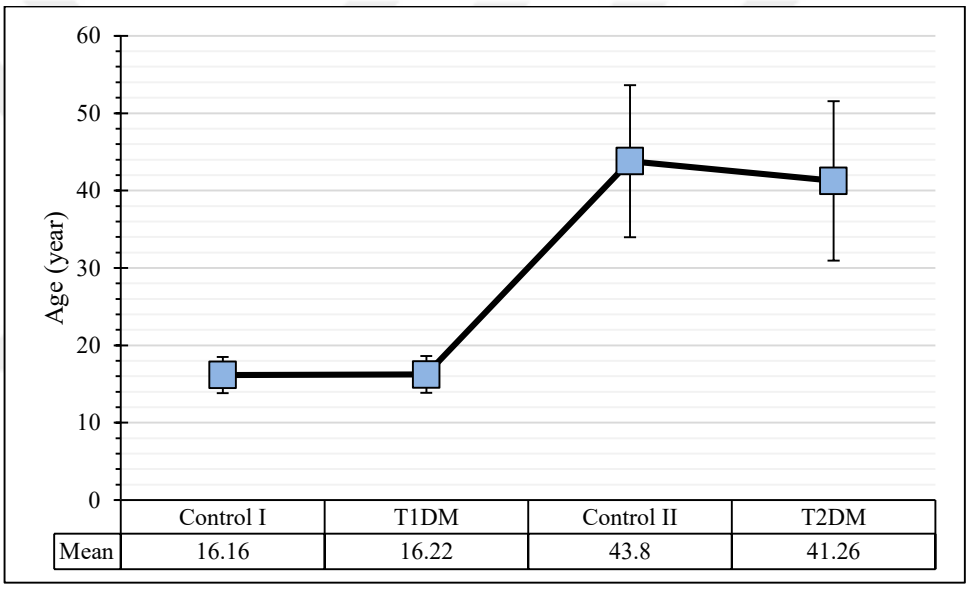

Figure 4.1 Age's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.2 Weight

The weight in Control I (52.00±5.10 kg) and T1DM women (44.70±7.10 kg), was non-significantly different (P>0.05). Moreover, the weight in Control II (62.28±5.82 kg), and T2DM women (76.06±16.22 kg), was also non-significantly different (P > 0.05). Nevertheless, the weight of T2DM women was (P<0.05) significantly higher than the weight of T1DM women (Figure 4.2).

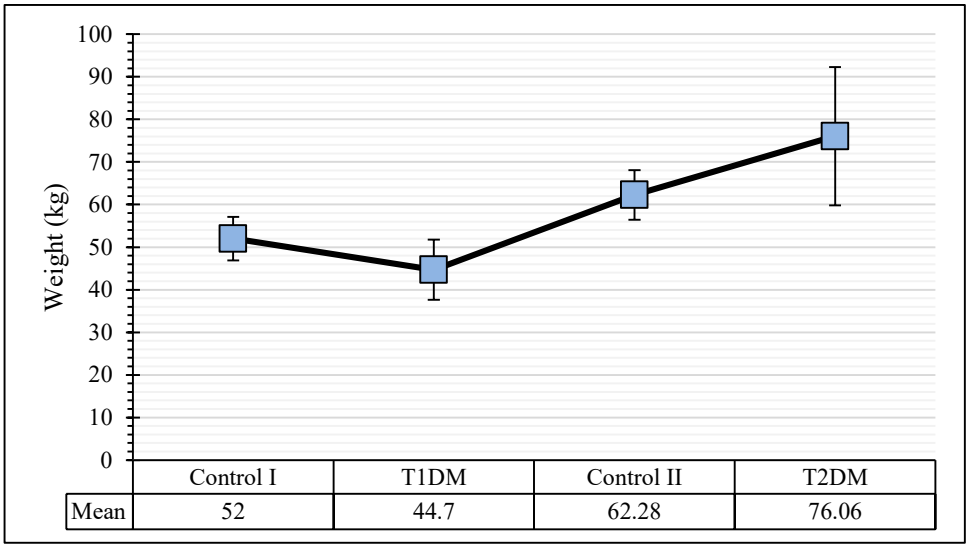

Figure 4.2 Weight's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.3 Height

The height in Control I (154.08±6.94 cm) and T1DM women (152.42±6.37 cm), was non-significantly different (P>0.05). Moreover, the height in Control II (160.96±4.18 cm), and T2DM women (160.00±4.71 cm), was also non-significantly different (P > 0.05). Nevertheless, the height of T2DM women was significantly (P < 0.05) higher than the height of T1DM women (Figure 4.3).

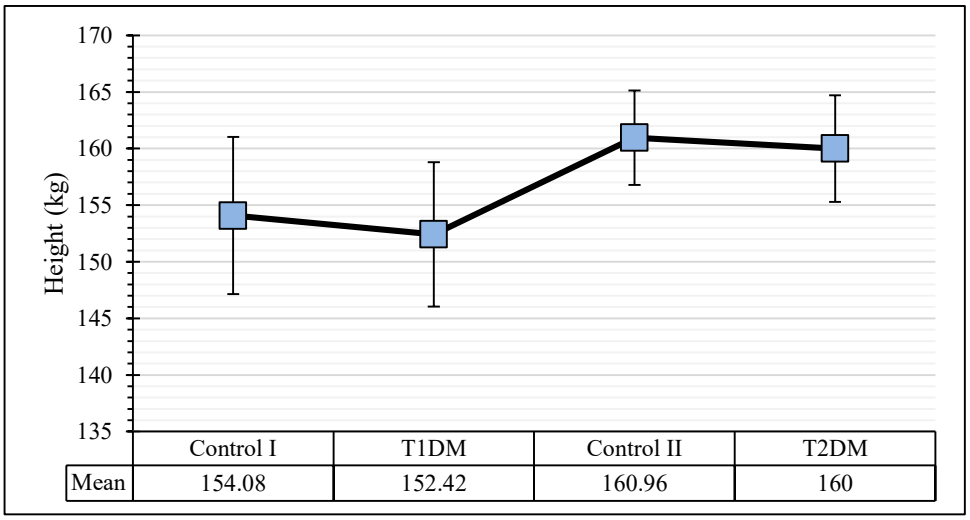

Figure 4.3 Height's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.4 Body Mass Index

The BMI in Control I (21.87±1.01 kg.m^{-2}) was significantly ($P < 0.05$) higher than T1DM women (19.19±2.63 kg.m^{-2}). Moreover, the BMI in Control II (24.05±2.25 kg.m^{-2}) was ($P < 0.05$) significantly lower than type two diabetes women (29.82±6.77 kg.m^{-2}). Nonetheless, the BMI of type two diabetes women was significantly ($P < 0.05$) higher than the BMI of T1DM women (Figure 4.4).

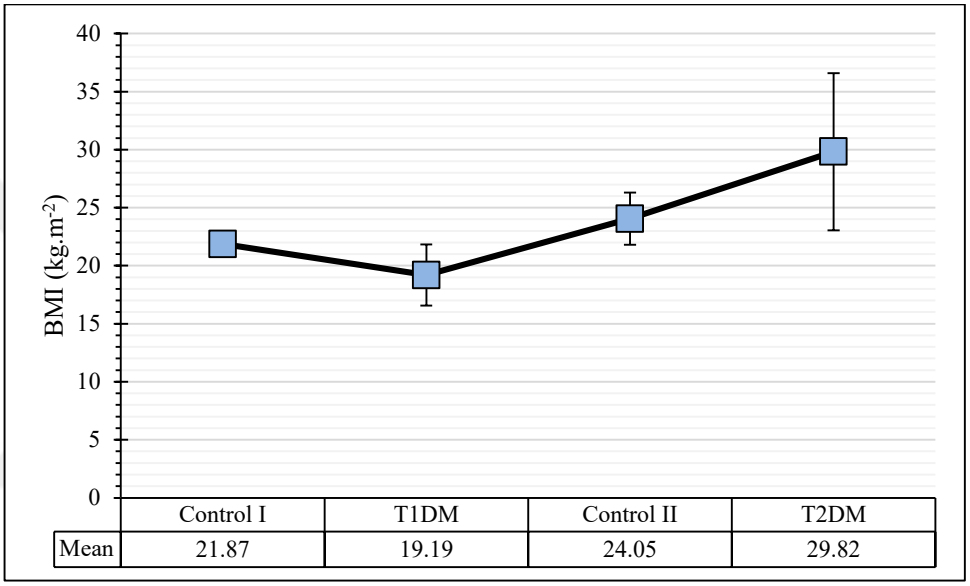

Figure 4.4 BMI's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.5 Leptin

The level of leptin in Control I (4.60±2.86 ng/mL) was significantly ($P<0.05$) lower than T1DM women (12.26±5.36 ng/mL). Moreover, the level of leptin in Control II (4.54±2.65 ng/mL) was significantly lower ($P<0.05$) than T2DM women (11.50±4.76 ng/mL). Nevertheless, the level of leptin in T2DM women was non-significantly ($P>0.05$) different compared to the level of leptin in T1DM women (Figure 4.5).

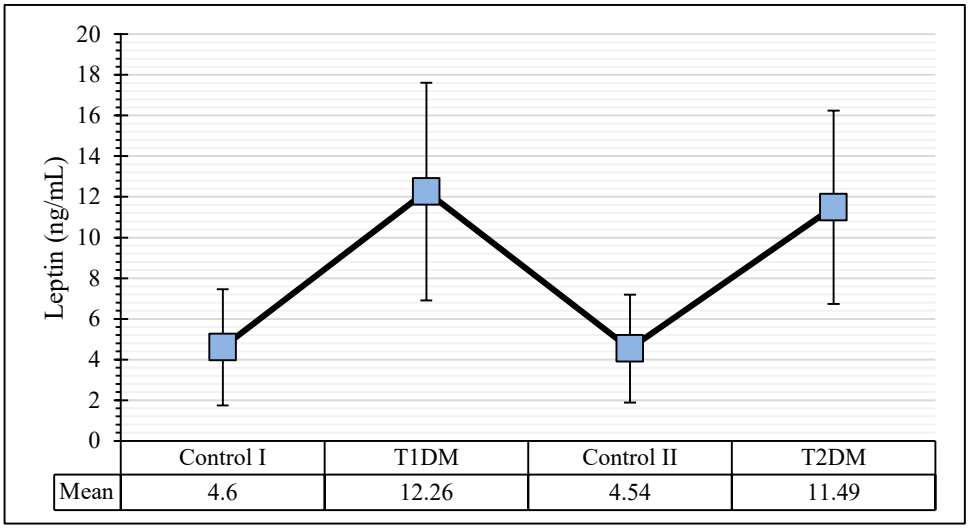

Figure 4.5 Leptin's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.6 Insulin

The level of insulin in Control I (9.41±2.46 mIU/L) was significantly (P<0.05) higher than T1DM women (2.25±1.17 mIU/L). Moreover, the level of insulin in Control II (10.31±2.68 mIU/L) was (P<0.05) significantly lower than T2DM women (14.93±3.89 mIU/L). Nevertheless, insulin levels in T2DM women was (P<0.05) significantly (Figure 4.6), higher than the level of insulin in T1DM women.

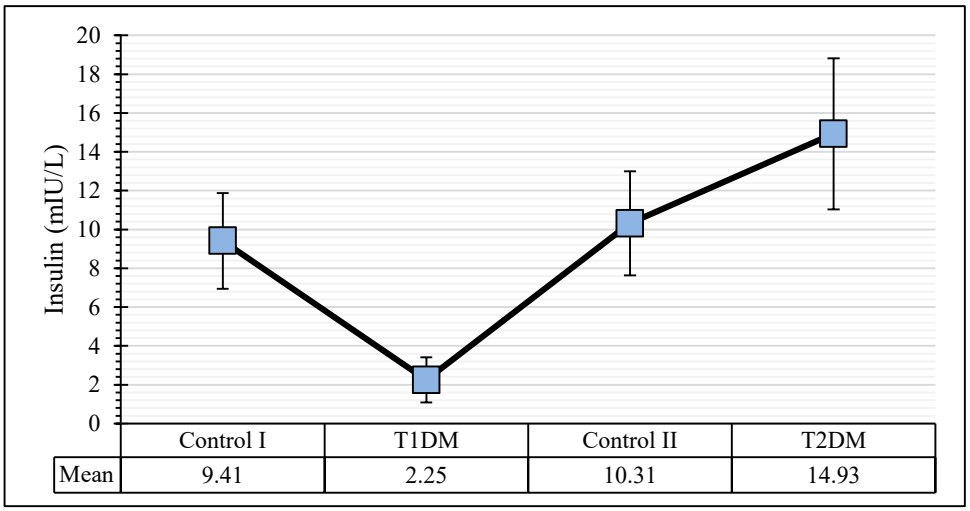

Figure 4.6 Insulin's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.7 Fasting Serum Glucose

The level of FSG in Control I (85.64±5.02 mg/dL) was (P< 0.05) significantly lower than T1DM women (149.58±17.61 mg/dL). Moreover, the level of FSG in Control II (91.24±5.14 mg/dL) was (P<0.05) significantly, lower than T2DM women (196.98±54.14 mg/dL). Nevertheless, in T2DM women the level of FSG was significantly (P< 0.05) (Figure 4.7), higher than the level of FSG in T1DM women.

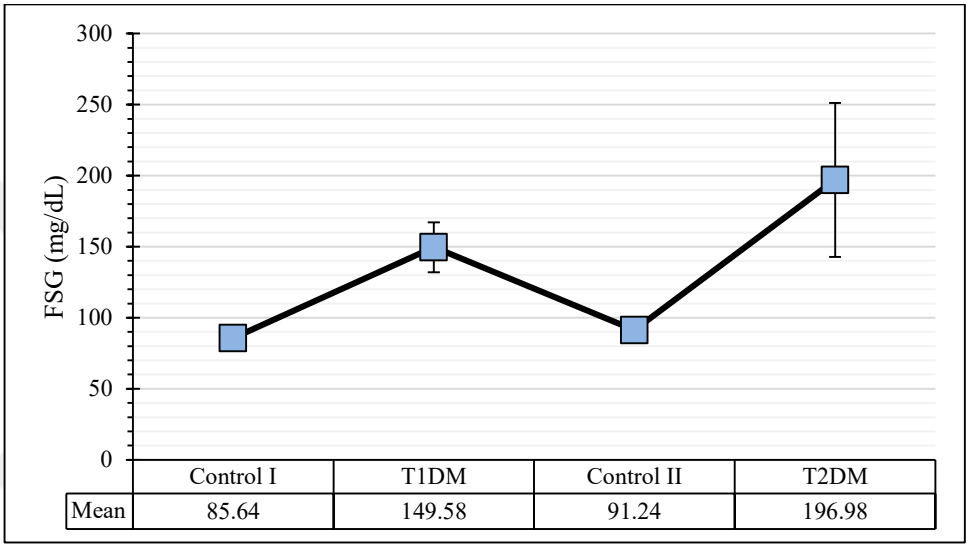

Figure 4.7 FSG's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.8 Glycated Hemoglobin

The level of HbA1c in Control I (4.73±0.32 %) was significantly (P<0.05) lower than T1DM women (7.08±1.13 %). Moreover, the level of HbA1c in Control II (4.81±0.35 %) was significantly lower (P<0.05) than T2DM women (8.53±1.49 %). Nevertheless, in T2DM women the level of HbA1c was (P< 0.05) significantly higher than the levels of HbA1c in T1DM women (Figure 4.8).

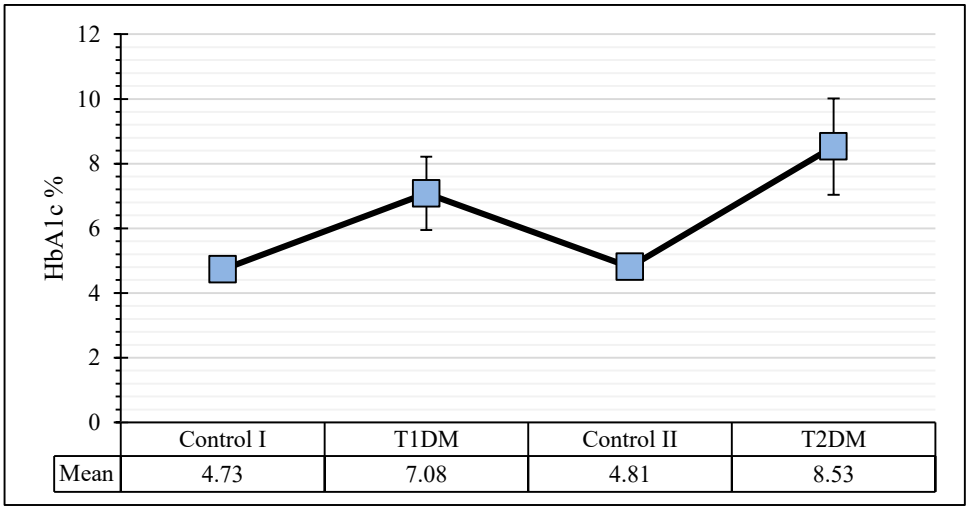

Figure 4.8 HbA1c's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.9 Total Cholesterol

The level of TC in Control I (138.84±16.08 mg/dL) and T1DM women (135.42±16.73 mg/dL), was (P>0.05) non-significantly different. Moreover, the TC levels in control II (140.96±16.30 mg/dL) was significantly lower (P<0.05) than T2DM women (226.28±51.99 mg/dL). Nevertheless, as show in (Figure 4.9) the levels of TC in T2DM women was (P<0.05) significantly higher than the TC levels in T1DM women.

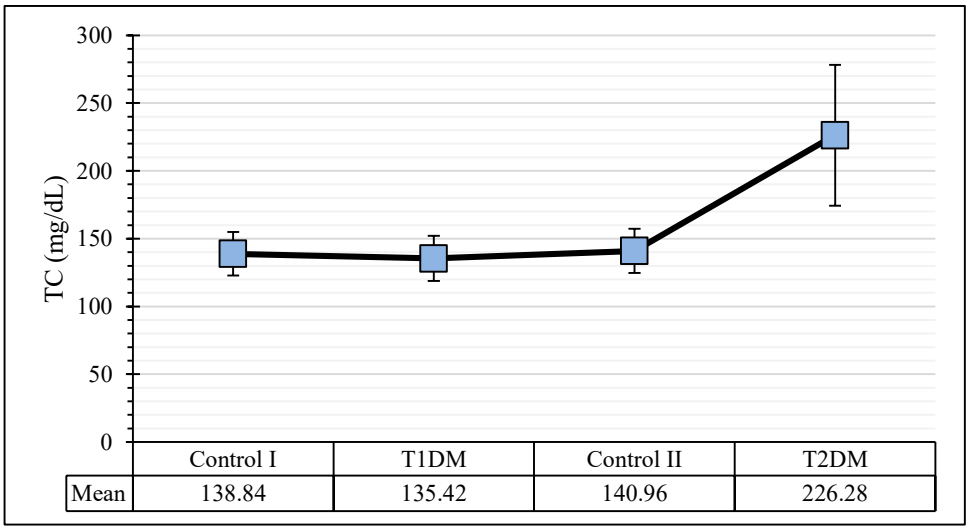

Figure 4.9 TC's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.10 Triglycerides

The level of TG in Control I (91.20±5.40 mg/dL) and T1DM women (90.44±8.41 mg/dL), was (P>0.05) non-significantly different. Moreover, the levels of TG in Control II (96.00±7.16 mg/dL) was (P<0.05) significantly lower than T2DM women (207.78±77.78 mg/dL). Nevertheless, as show in (Figure 4.10) the TG levels in T2DM women was (P<0.05) significantly, higher than the level of TG in T1DM women.

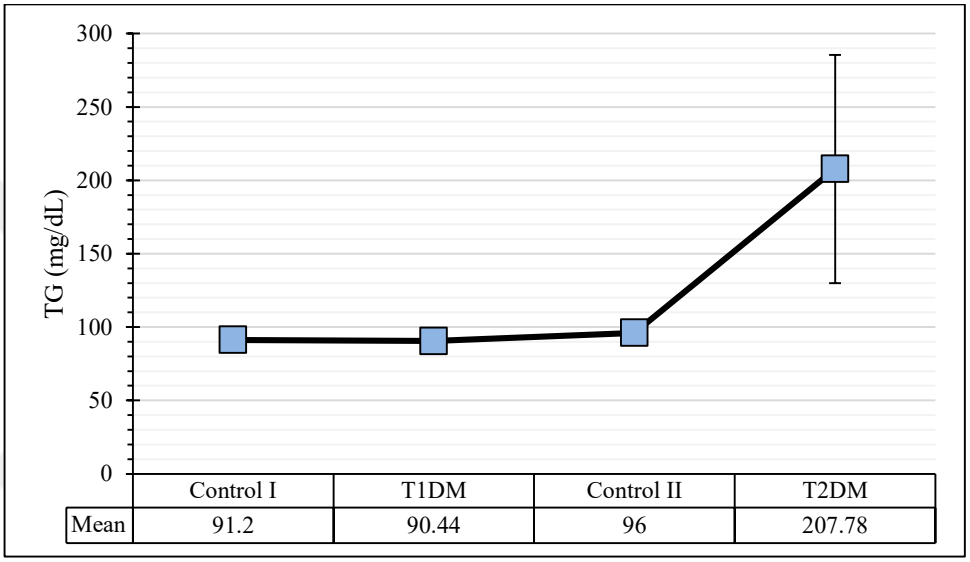

Figure 4.10 TG's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.11 High-Density Lipoprotein-Cholesterol

The level of HDL-C in Control I (53.71±4.65 mg/dL) was significantly higher (P<0.05) T1DM women (46.87±5.90 mg/dL). Moreover, the level of HDL-C in Control II (51.66±5.43 mg/dL) was significantly higher (P<0.05) than T2DM women (39.05±4.61 mg/dL). Nevertheless, as shown in (Figure 4.11), the HDL-C levels in T2DM women was (P<0.05) significantly lower than the level of HDL-C in T1DM women.

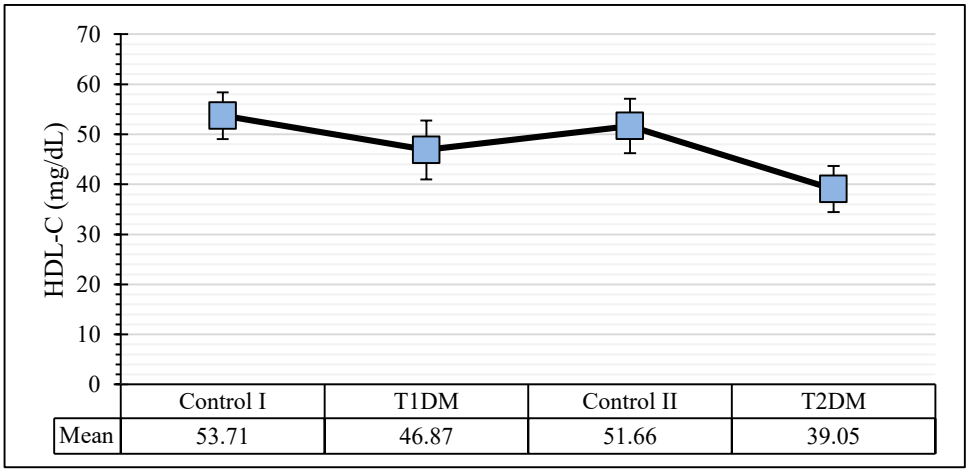

Figure 4.11 HDL-C's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.12 Low-Density Lipoprotein-Cholesterol

The level of LDL-C in Control I (66.89±16.94 mg/dL) and (70.46±16.99 mg/dL) in T1DM women, was (P>0.05) non-significantly different. Moreover, the LDL-C levels in Control II (70.10±18.53 mg/dL) was significantly lower (P< 0.05) than T2DM women (145.67±52.98 mg/dL). Nevertheless, as show in (Figure 4.12) the level of LDL-C in T2DM women was (P<0.05) significantly, higher than the levels of LDL-C in T1DM women.

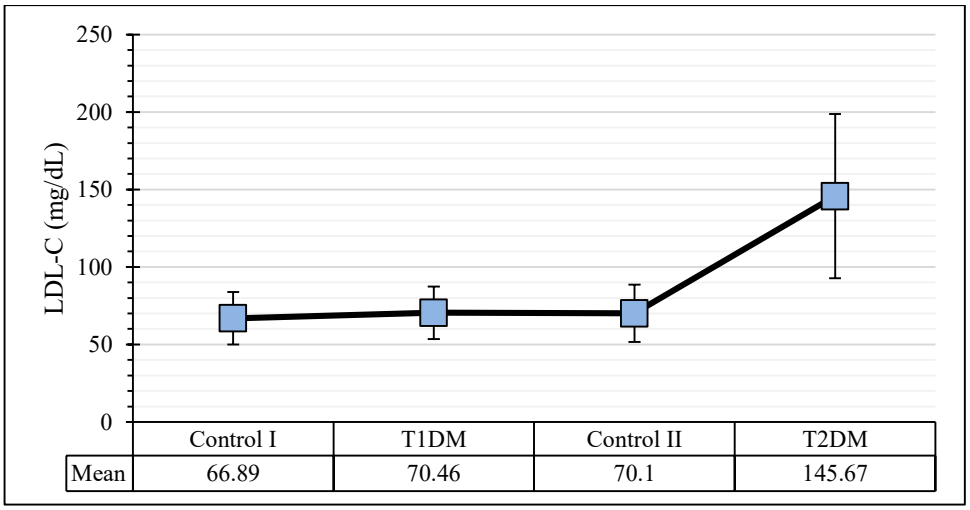

Figure 4.12 LDL-C's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.13 Very Low-Density Lipoprotein-Cholesterol

The level of VLDL-C in Control I (18.24±1.08 mg/dL) and (18.09±1.68 mg/dL) in T1DM women, was non-significantly (P>0.05) different. Moreover, the level of VLDL-C in Control II (19.20±1.43 mg/dL) was significantly (P<0.05), lower than T2DM women (41.56±15.56 mg/dL). Nevertheless, as show in (Figure 4.13) the VLDL-C levels in T2DM women was (P<0.05) significantly, higher than the level of VLDL-C in T1DM women.

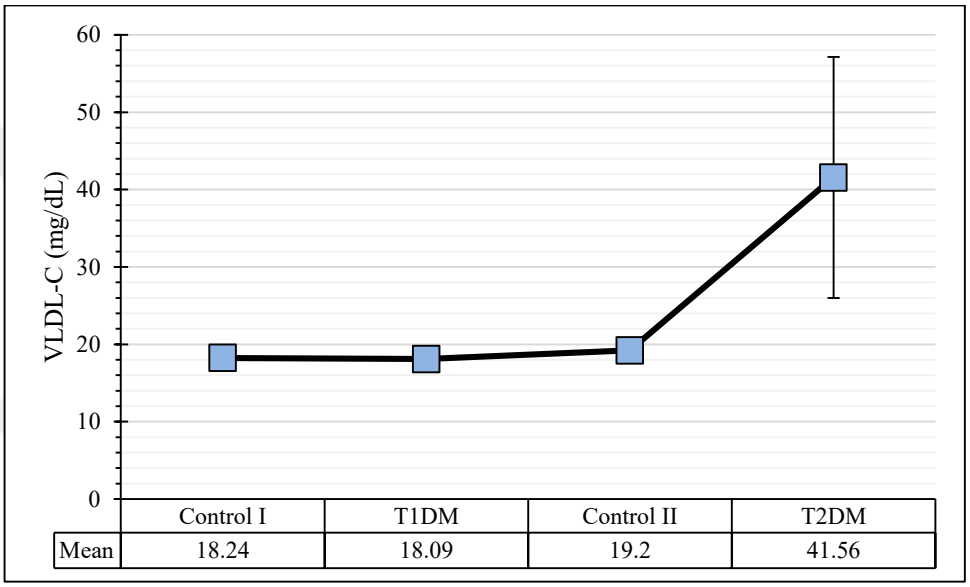

Figure 4.13 VLDL-C's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.14 C-Reactive Protein

The level of CRP in Control I (0.24±0.13 mg/dL) was (P<0.05) significantly lower T1DM women (0.39±0.23 mg/dL). Moreover, the level of CRP in Control II (0.25±0.15 mg/dL) was significantly lower (P<0.05) than T2DM women (0.56±0.39 mg/dL). Nevertheless, the levels of CRP in T2DM women was significantly (P<0.05), higher than the level of CRP in T1DM women (Figure 4.14).

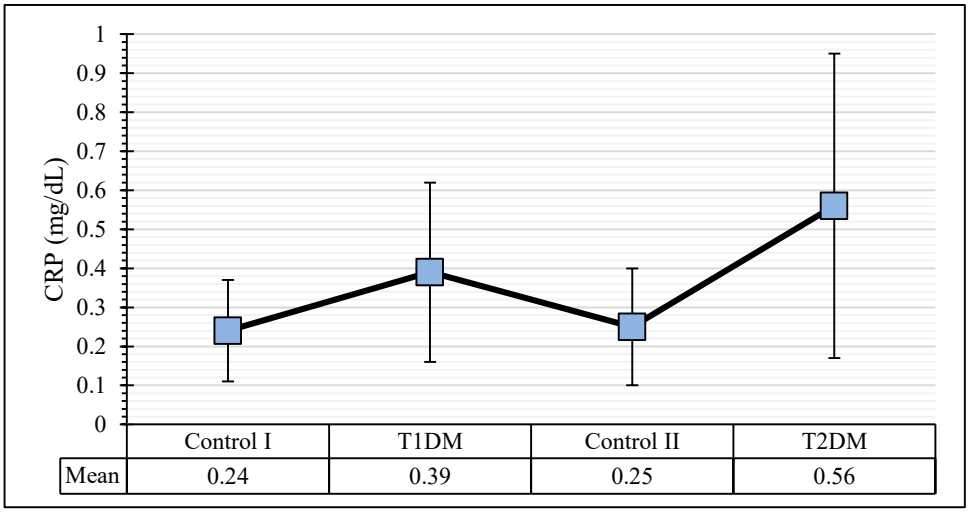

Figure 4.14 CRP's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.15 Ghrelin

The level of ghrelin in Control I (6.76±1.69 ng/mL) was significantly higher (P<0.05) T1DM women (3.69±1.92 ng/mL). Moreover, the level of ghrelin in Control II (6.46±1.57 ng/mL) was significantly higher (P<0.05) than T2DM women (3.47±1.98 ng/mL). Nevertheless, as show in (Figure 4.15), the level of ghrelin in T2DM women was non-significantly (P>0.05) different compared to the level of ghrelin in T1DM women.

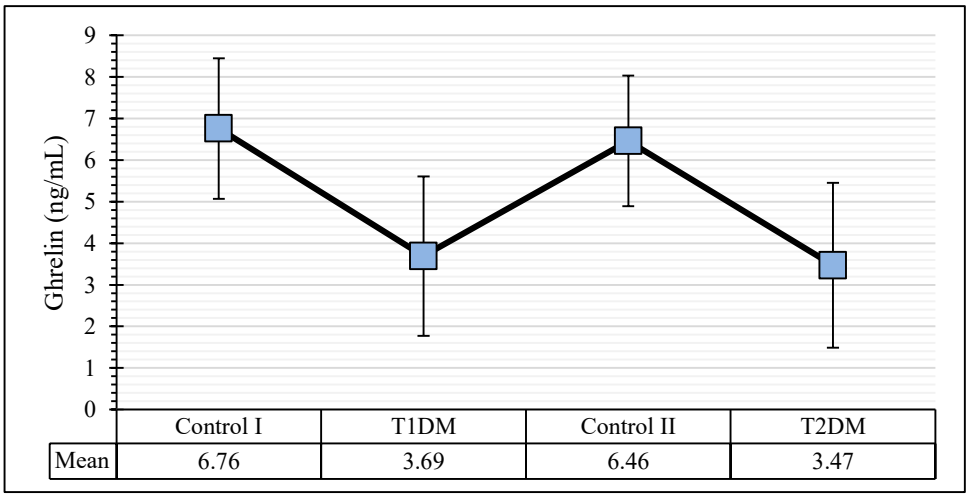

Figure 4.15 Ghrelin's mean (square) in T1DM, T2DM and the corresponding control subjects (I and II), and the SD (error bar)

4.16 Correlation in T1DM

The association of chosen parameters (leptin, insulin, HbA1c, and ghrelin), as show in (Table 4.1), were investigated by using Pearson's correlation (r) with the other parameters of this study in women with T1DM.

Table 4.1 Correlation in T1DM

VARIABLE	LEPTIN		INSULIN		HbA1c		GHRELIN	
	r	*P*	r	*P*	r	*P*	r	*P*
Insulin	-0.084	0.561	-	-	0.154	0.286	0.036	0.804
HbA1c	0.044	0.760	0.154	0.286	-	-	0.146	0.311
Ghrelin	-0.135	0.352	0.036	0.804	0.146	0.311	-	-
FSG	0.098	0.499	0.071	0.622	0.665*	<0.001	0.171	0.235
TC	-0.015	0.915	-0.064	0.660	0.047	0.747	-0.119	0.412
TG	-0.240	0.094	-0.073	0.614	-0.072	0.618	-0.034	0.815
HDL-C	-0.115	0.425	0.277	0.052	0.303*	0.033	0.199	0.166
LDL-C	0.049	0.737	-0.152	0.293	-0.052	0.720	-0.183	0.204
VLDL-C	-0.240	0.094	-0.073	0.614	-0.072	0.618	-0.034	0.815
CRP	-0.093	0.520	-0.141	0.330	-0.053	0.713	-0.129	0.371
Age	0.057	0.694	0.089	0.538	0.073	0.613	0.281*	0.048
Weight	0.337*	0.017	-0.318*	0.025	-0.143	0.322	0.175	0.224
Height	-0.004	0.977	-0.104	0.471	-0.109	0.450	0.413*	0.003
BMI	0.394*	0.005	-0.300*	0.034	-0.120	0.407	-0.034	0.813

* Significant at $P<0.05$

In women with T1DM, leptin has shown positive weak correlation with weight (r=0.337, P=0.017; Figure 4.16), and positive weak correlation with BMI (r=0.394, P=0.005; Figure 4.17).

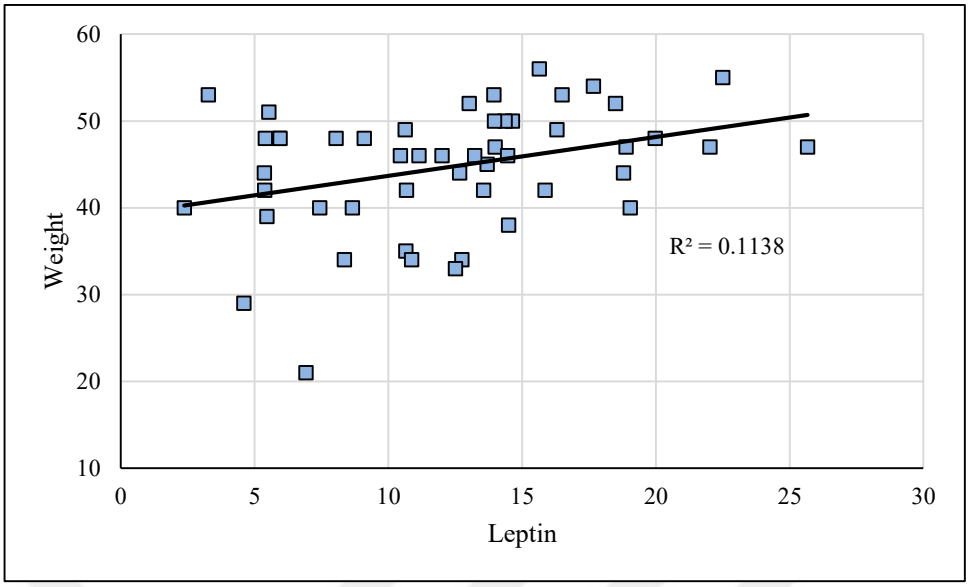

Figure 4.16 Correlation between leptin and weight in women with T1DM

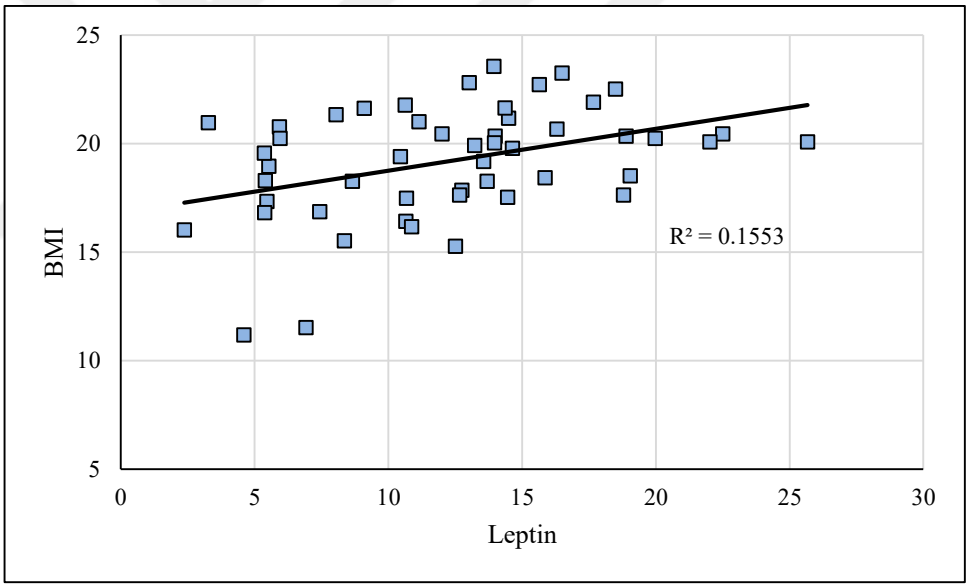

Figure 4.17 Correlation between leptin and BMI in women with T1DM

In women with T1DM, insulin has shown negative weak correlation with weight (r=-0.318, *P*=0.025; Figure 4.18), and negative weak correlation with BMI (r=-0.300, *P*=0.034; Figure 4.19).

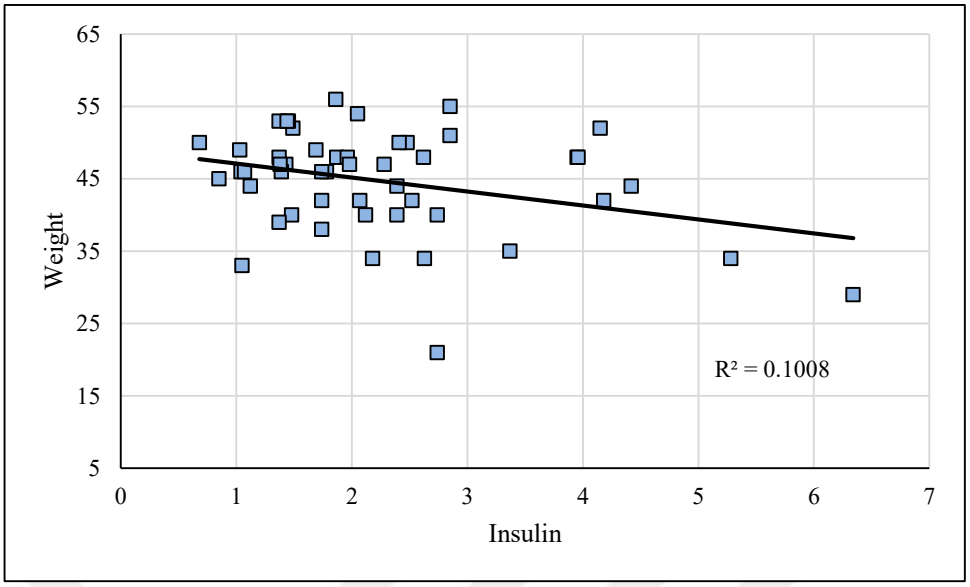

Figure 4.18 Correlation between insulin and weight in women with T1DM

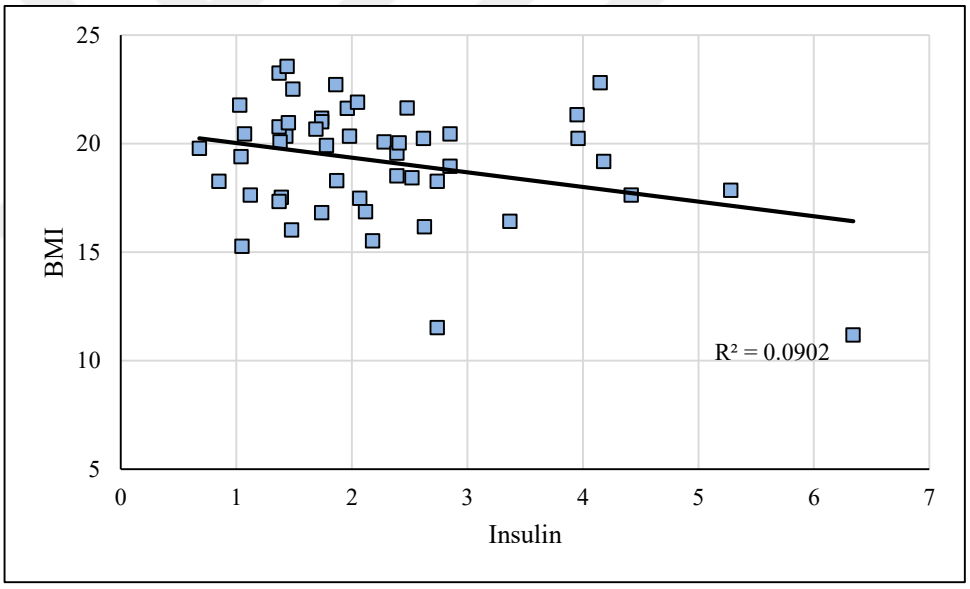

Figure 4.19 Correlation between insulin and BMI in women with T1DM

In women with T1DM, HbA1c has shown positive moderate correlation with FSG (r=0.665, *P*<0.001) (Figure 4.20), as wall as positive weak correlation with the HDL-C (r=0.303, *P*=0.033) (Figure 4.21).

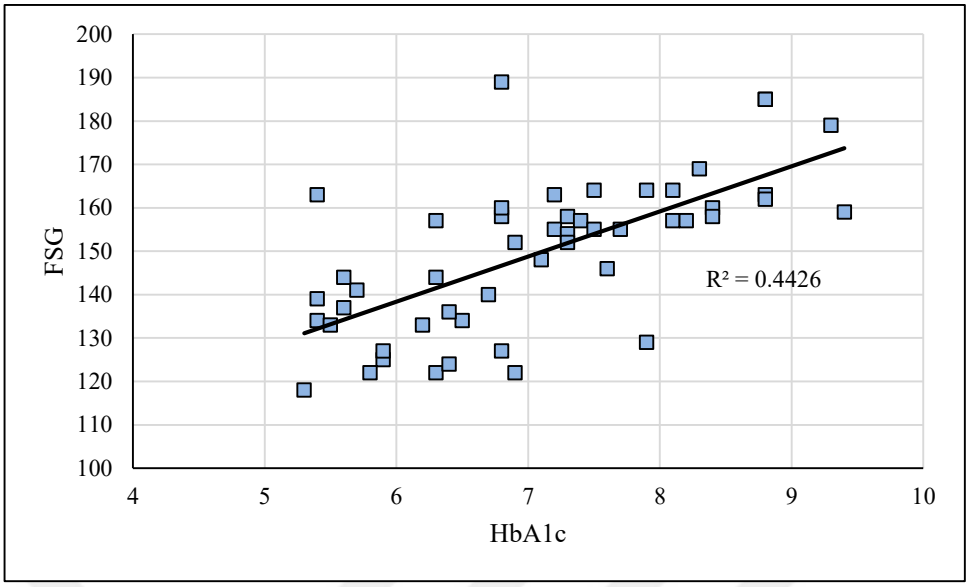

Figure 4.20 Correlation between HbA1c and FSG in women with T1DM

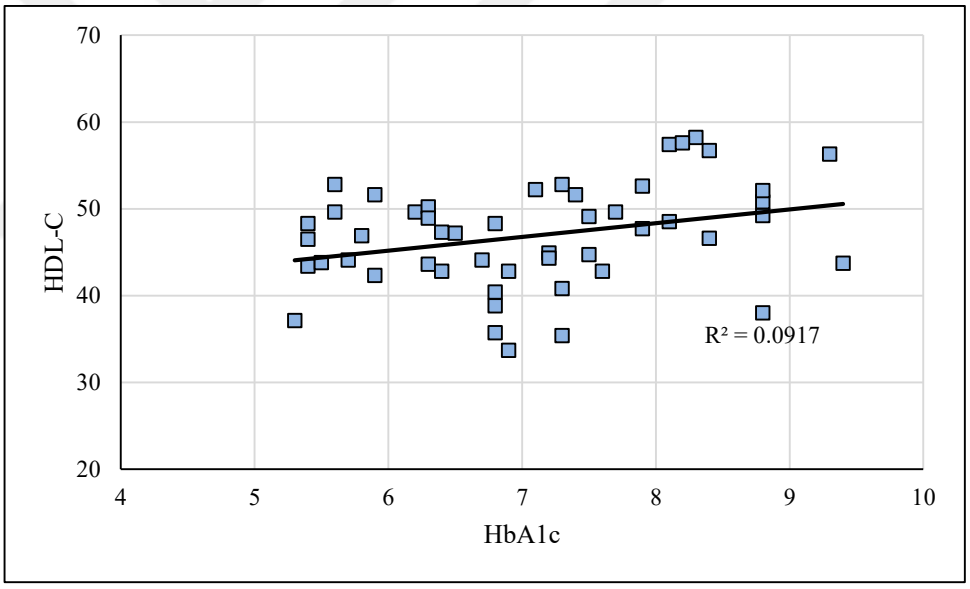

Figure 4.21 Correlation between HbA1c and HDL-C in women with T1DM

In women with T1DM, ghrelin has shown positive weak correlation with age (r=0.281, *P*=0.048; Figure 4.22), and positive weak correlation with height (r=0.413, *P*=0.003; Figure 4.23).

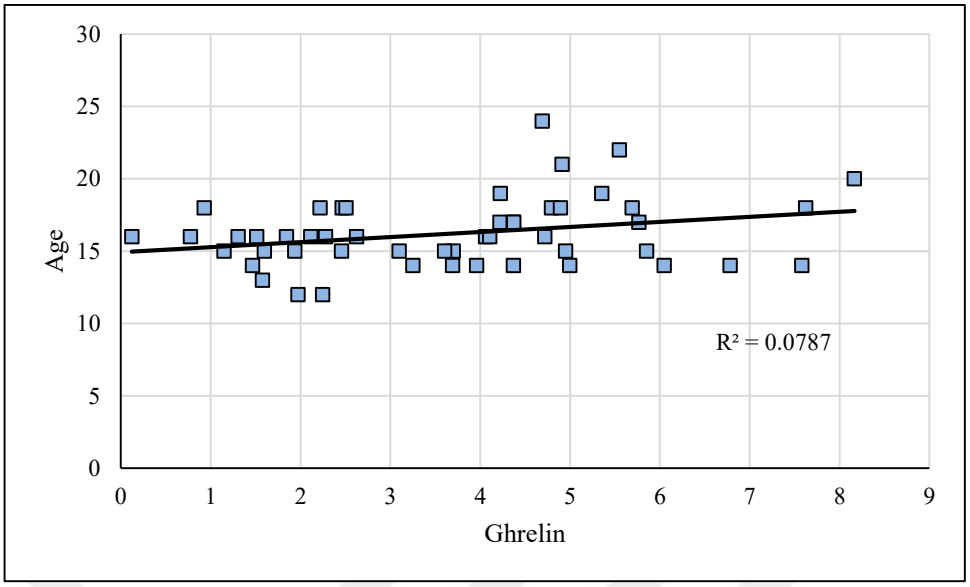

Figure 4.22 Correlation between ghrelin and age in women with T1DM

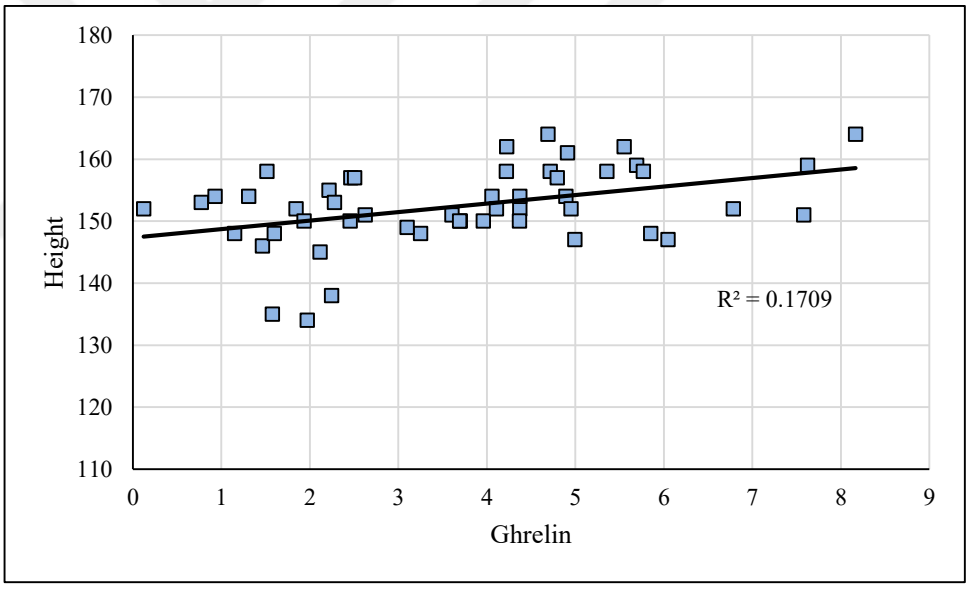

Figure 4.23 Correlation between ghrelin and height in women with T1DM

4.17 Correlation in T2DM

The association of chosen parameters (leptin, insulin, HbA1c, and ghrelin) as show in (Table 4.2), were investigated by using Pearson's correlation (r) with the other parameters of this study in women with T2DM.

Table 4.2 Correlation in T2DM

VARIABLE	LEPTIN		INSULIN		HbA1c		GHRELIN	
	r	*P*	r	*P*	r	*P*	r	*P*
Insulin	0.339*	0.016	-	-	-0.335*	0.017	-0.188	0.191
HbA1c	-0.096	0.509	-0.335*	0.017	-	-	0.083	0.566
Ghrelin	-0.433*	0.002	-0.188	0.191	0.083	0.566	-	-
FSG	-0.072	0.621	-0.229	0.109	0.739*	<0.001	0.096	0.509
TC	0.409*	0.003	0.256	0.072	-0.105	0.469	-0.262	0.066
TG	0.101	0.487	0.120	0.407	0.012	0.937	-0.084	0.560
HDL-C	-0.086	0.553	0.052	0.717	-0.112	0.437	0.133	0.358
LDL-C	0.379*	0.007	0.212	0.140	-0.096	0.505	-0.244	0.087
VLDL-C	0.101	0.487	0.120	0.407	0.012	0.937	-0.084	0.560
CRP	0.165	0.253	0.080	0.583	0.251	0.078	-0.234	0.102
Age	-0.018	0.901	0.010	0.942	-0.0235	0.100	0.190	0.185
Weight	0.418*	0.003	-0.014	0.924	0.081	0.574	-0.506*	<0.001
Height	-0.366*	0.009	0.061	0.673	-0.041	0.777	0.301*	0.034
BMI	0.483*	<0.001	-0.033	0.822	0.084	0.561	-0.547*	<0.001

* Significant at $P<0.05$

In women with T2DM, leptin has shown positive weak correlation with insulin (r=0.339, *P*=0.016; Figure 4.24), negative weak correlation with ghrelin (r=-0.433, *P*=0.002; Figure 4.25), positive weak correlation with TC (r=0.409, *P*=0.003; Figure 4.26), positive weak correlation with LDL-C (r=0.379, *P*=0.007; Figure 4.27), positive weak correlation with weight (r=0.418, *P*=0.003; Figure 4.28), negative weak correlation with height (r=-0.366, *P*=0.009; Figure 4.29), and positive weak correlation with BMI (r=0.483, *P*<0.001; Figure 4.30).

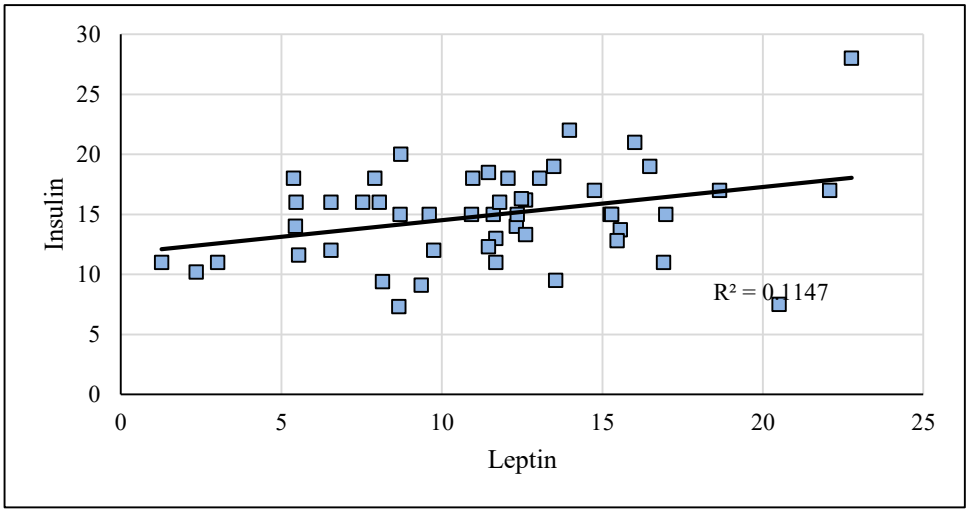

Figure 4.24 Correlation between leptin and insulin in women with T2DM

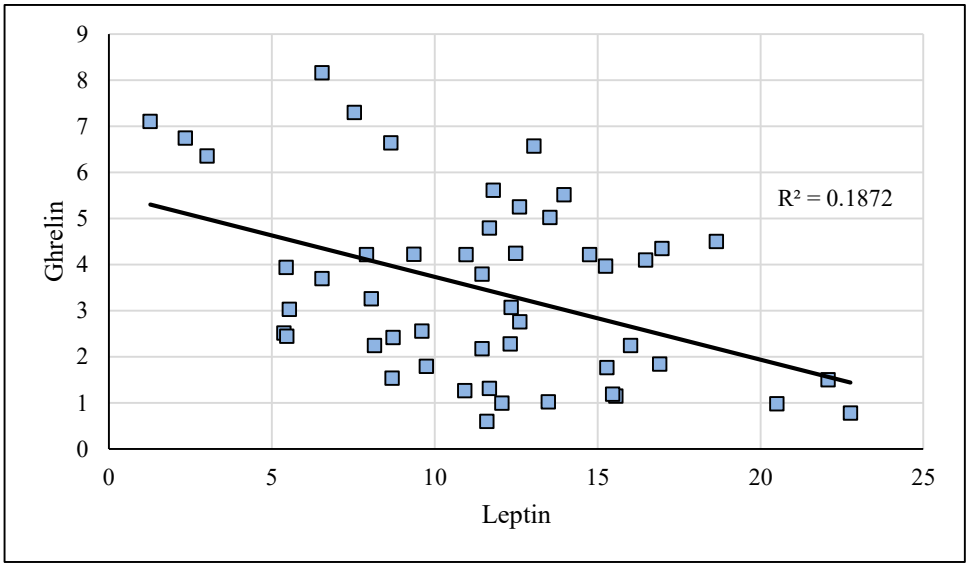

Figure 4.25 Correlation between leptin and ghrelin in women with T2DM

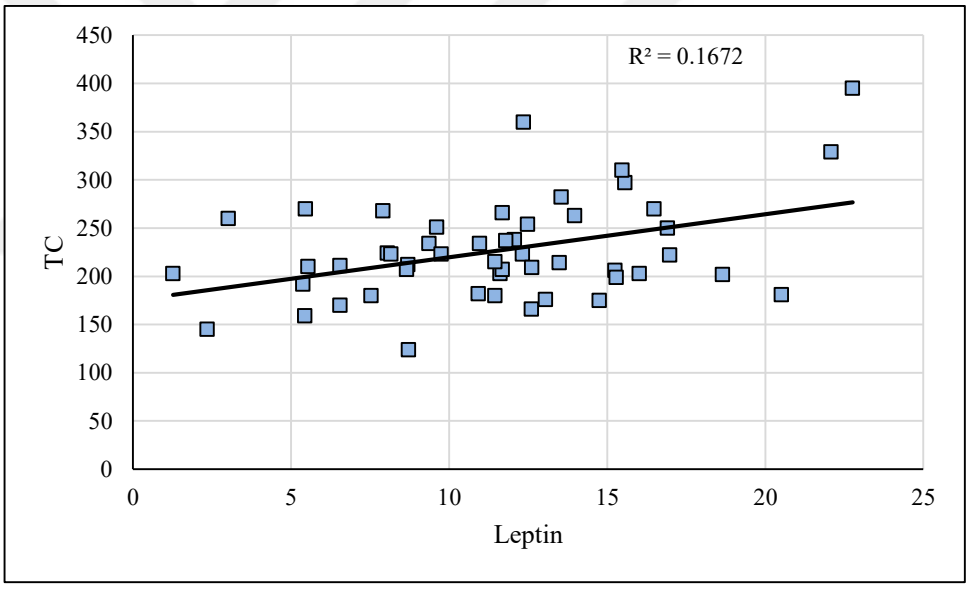

Figure 4.26 Correlation between leptin and TC in women with T2DM

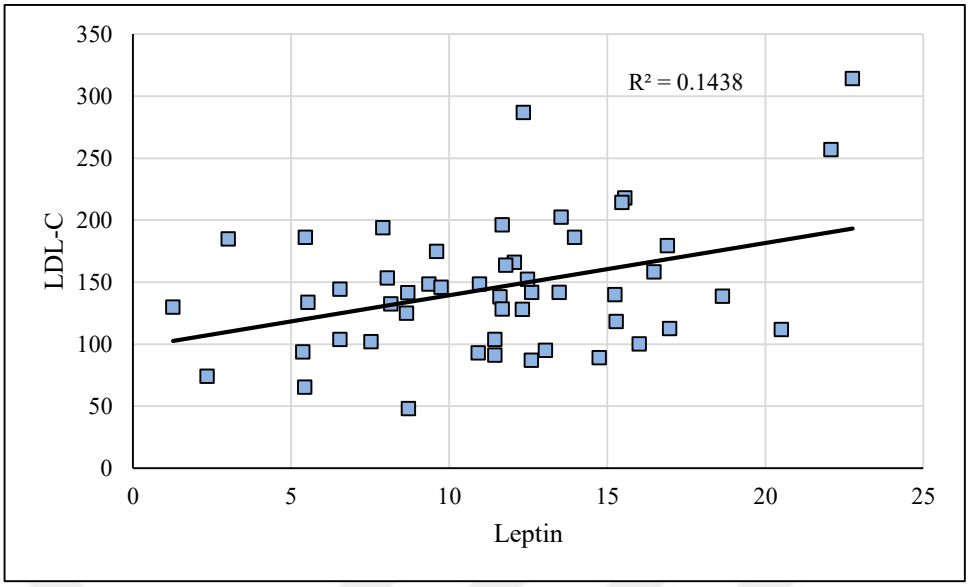

Figure 4.27 Correlation between leptin and LDL-C in women with T2DM

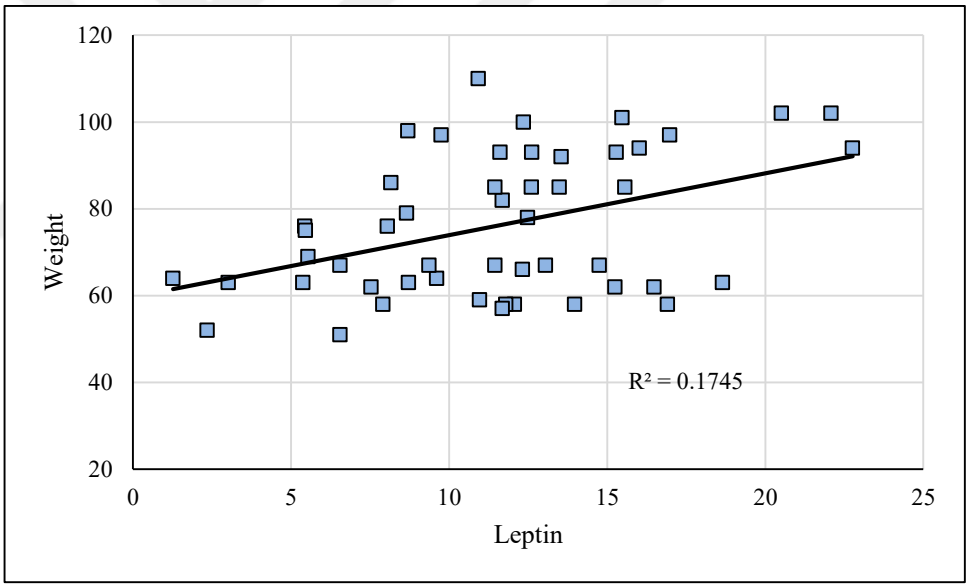

Figure 4.28 Correlation between leptin and weight in women with T2DM

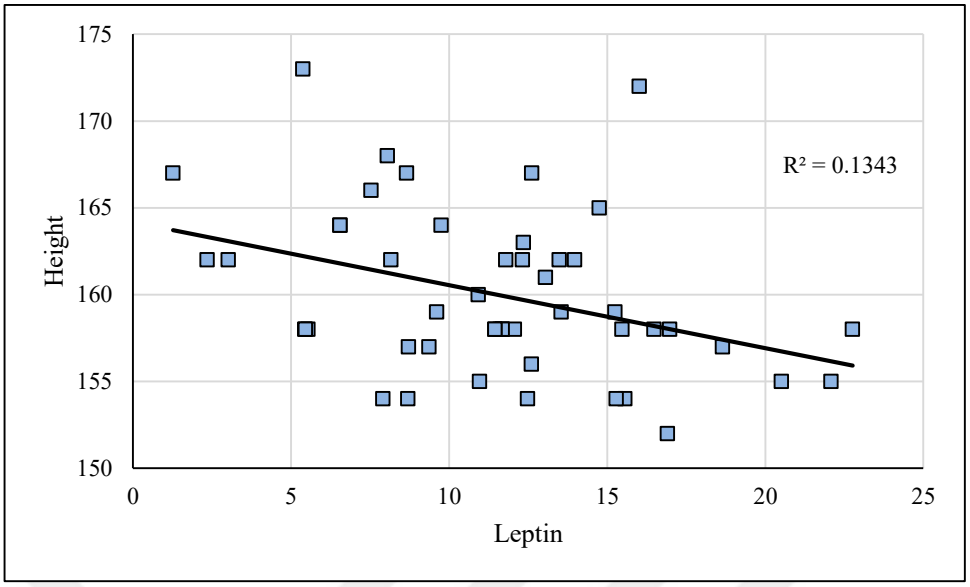

Figure 4.29 Correlation between leptin and height in women with T2DM

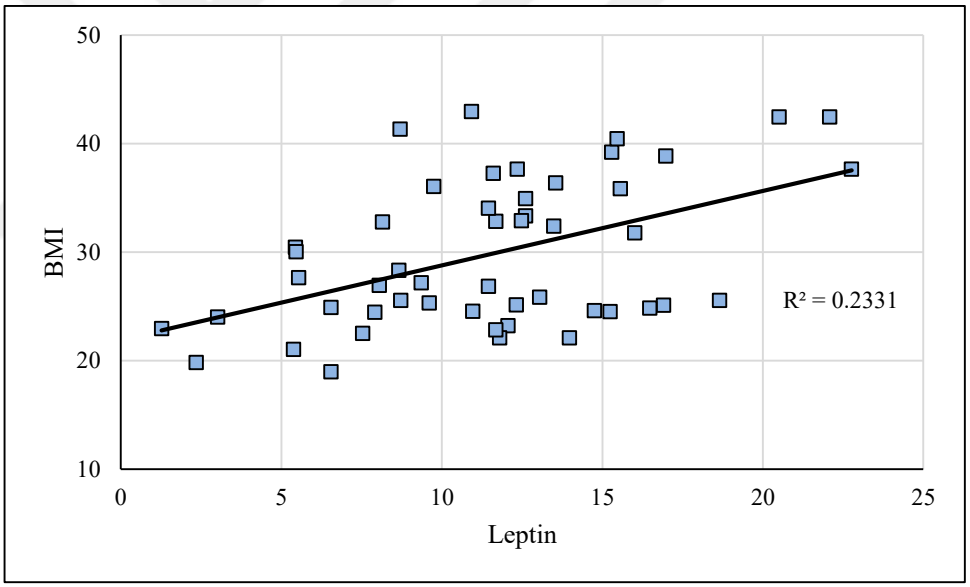

Figure 4.30 Correlation between leptin and BMI in women with T2DM

In women with T2DM, insulin has shown negative weak correlation with HbA1c (r=-0.335, *P*=0.017; Figure 4.31).

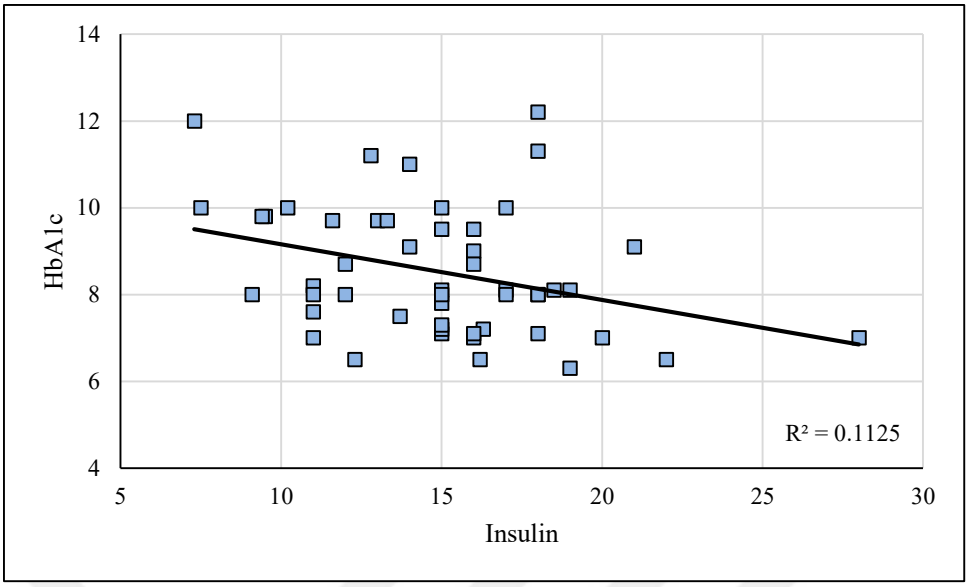

Figure 4.31 Correlation between insulin and HbA1c in women with T2DM

In women with T2DM, HbA1c has shown positive strong correlation with FSG (r=0.739, *P*<0.001; Figure 4.32).

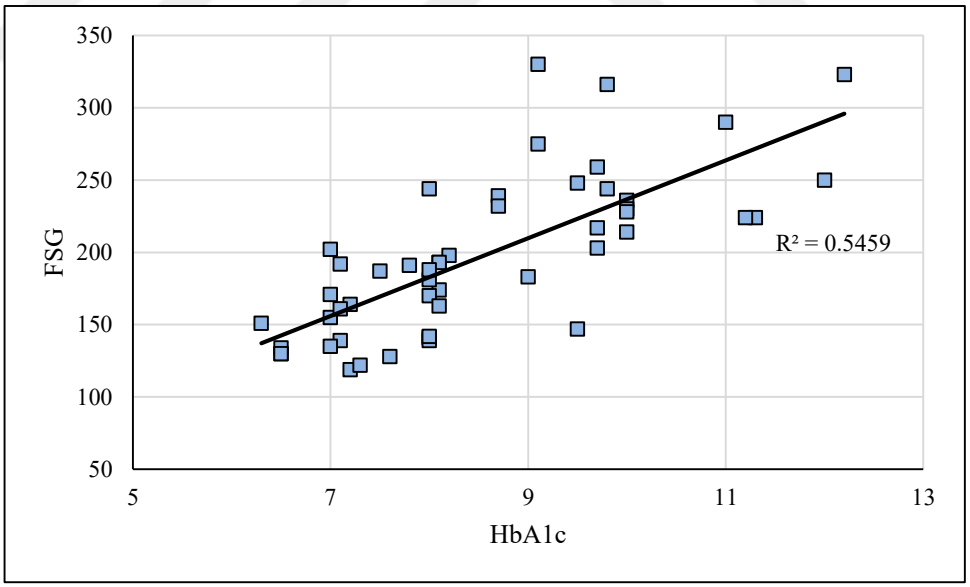

Figure 4.32 Correlation between HbA1c and FSG in women with T2DM

In women with T2DM, ghrelin has shown negative moderate correlation with weight (r=-0.506, *P*<0.001; Figure 4.33), positive weak correlation with height (r=0.301, *P*=0.034;

Figure 4.34), and negative moderate correlation with BMI (r=-0.547, *P*<0.001; Figure 4.35).

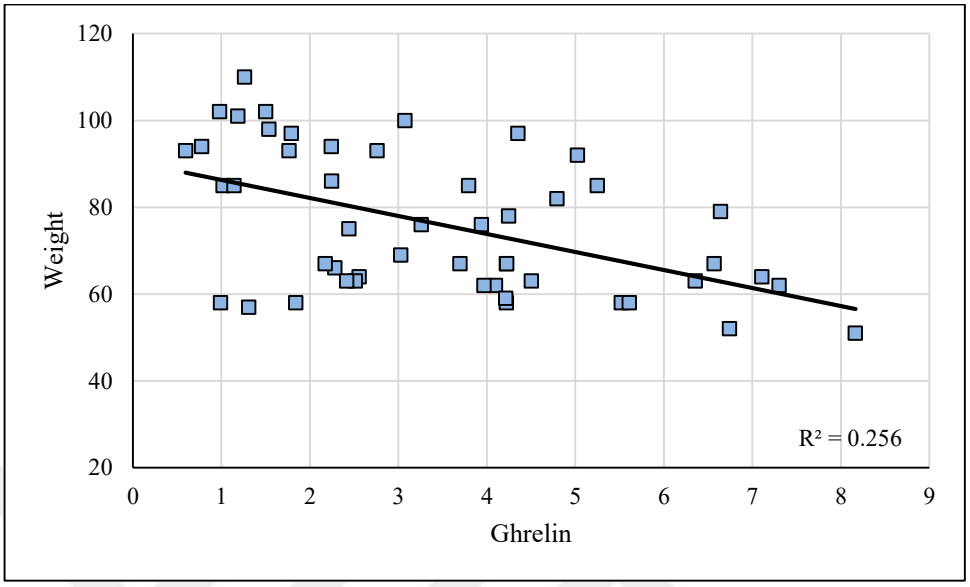

Figure 4.33 Correlation between ghrelin and weight in women with T2DM

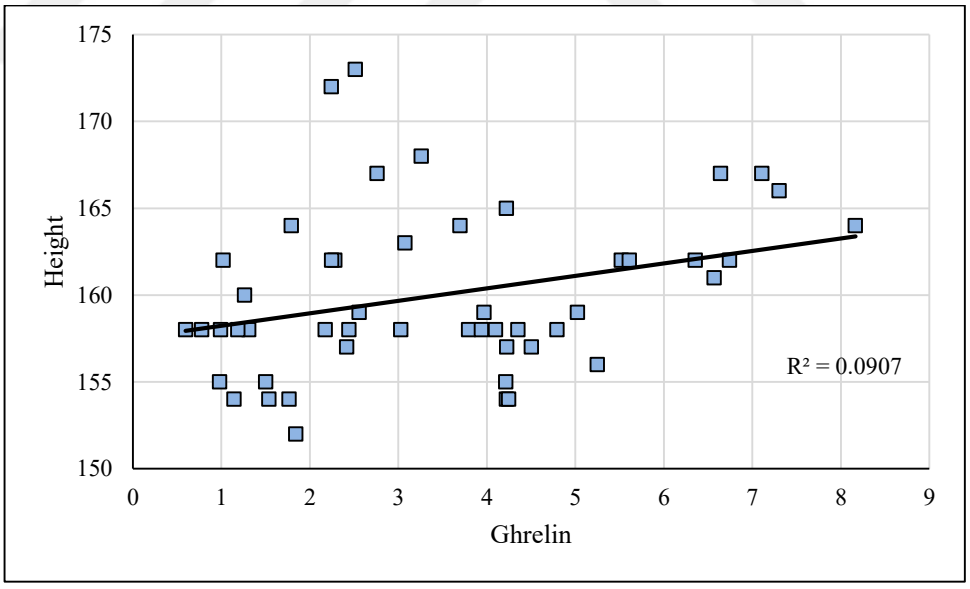

Figure 4.34 Correlation between ghrelin and height in women with T2DM

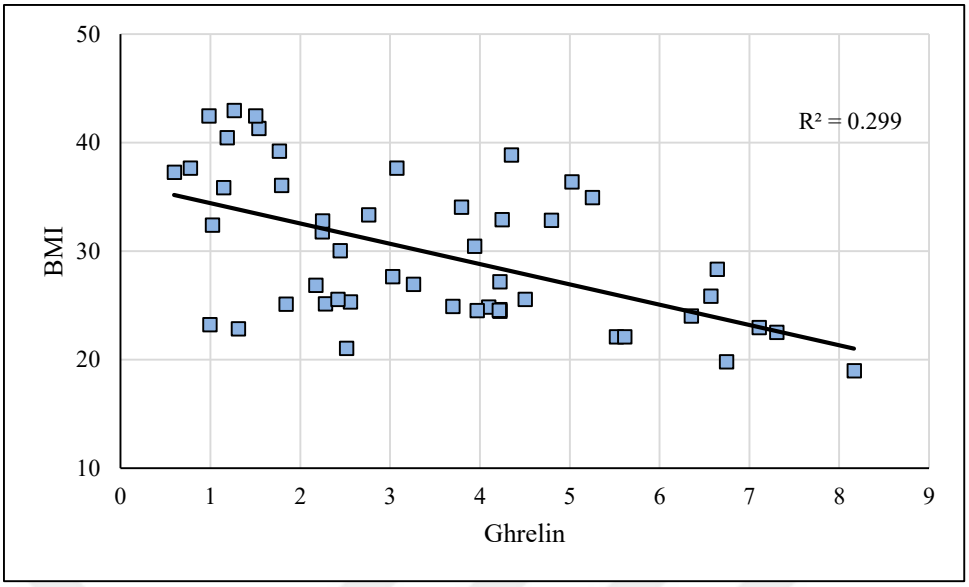

Figure 4.35 Correlation between ghrelin and BMI in women with T2DM

5. DISCUSSION

The present study has attempted to discover the relationship between insulin and leptin in type 1 and type 2 diabetes mellitus in women as the main goal. Additionally, the study was proceeded by testing ghrelin, lipid profile, and CRP differences between healthy women and diseased women (T1DM and T2DM). In this regard, two groups of healthy women were selected based on their age to control T1DM and T2DM women.

The weight and height of women with T1DM and their control were non-significantly different, and the same was observed in women with T2DM and their control. Nevertheless, the BMI of T1DM women was lower than control, while BMI of T2DM women was higher than control. The weight loss in T1DM was previously reported (Chetan *et al.* 2019, Conway *et al.* 2010), as in T1DM the reduction of insulin causes a reduction in the entry of glucose to the adipose tissue and therefore a reduced energy production which can cause weight loss (Musil *et al.* 2015). In T2DM, several studies have reported high BMI associates with the disease (Yaturu, 2011, Mehdi *et al.* 2012).

The level of insulin was reduced in T1DM, with an increase in HbA1c and FSG compared to the control. Furthermore, insulin was increased with HbA1c and FSG in women with T2DM disease. The differences in T1DM are logical and matched with the original definition of T1DM. The reduction of insulin as a consequence of beta-cell dysfunction in the pancreas results in the elevated glucose in the circulation, which in turn increases the percentage of glycated hemoglobin with time (Kakleas *et al.* 2015). In T2DM, insulin resistance is the major cause of elevated glucose even at sufficient quantities of insulin hormone (Goldstein, 2002). At both T1DM and T2DM, the patients in this study have shown poor glycemic control.

Leptin was increased significantly in women with T1DM and women with T2DM disease. Verrotti *et al.* have reported that patients with T1DM has shown non-significant differences in plasma leptin level compared to control (Verrotti *et al.* 1998), which disagrees with our results. In another study, Gilliam *et al.* have also reported a

similar leptin level in patients with T1DM compared to healthy people of similar BMI values (Gilliam *et al.* 2006). Iacobellis *et al.* have reported that T1DM patients have higher serum leptin levels compared to healthy people, which agrees with our results (Iacobellis *et al.* 2014). In the study of Mohammadzadeh and Zarghami, the authors have reported a significant reduction of leptin level in lean T2DM patients (Mohammadzadeh and Zarghami, 2013). The last study is disagreed with our study, yet in our study T2DM women were having higher BMI values compared to control.

Lipid profile parameters were not changed in T1DM women except for HDL-C, but they were significantly changed in women with T2DM disease. Feitosa *et al.* have reported that patients with T1DM have exhibited significant lower cholesterol and LDL levels compared to healthy people, while HDL and TG were similar to healthy people (Feitosa *et al.* 2013). Also Mehdi *et al.* have reported that patients with T2DM have exhibited significant higher levels of VLDL, TC, LDL, TG, while the HDL levels was significantly reduced (Mehdi *et al.* 2012).

The level of Ghrelin was reduced significantly in women with T1DM and women with T2DM compared to the corresponding control. Polkowska *et al.* have reported that levels of ghrelin was reduced in patients with T1DM (Polkowska *et al.* 2016), which agrees with our results. Soriano-Guillén *et al.* have reported significant reduction of ghrelin level in T1DM patients (Soriano-Guillén *et al.* 2004). El-Morsi *et al.* have mentioned that ghrelin level was increased in the plasma of T1DM patients (Aboul-Fotoh *et al.* 2011), which disagrees with our results. Poykko *et al.* have reported that ghrelin level was reduced in T2DM patients, and also negative correlation was observed between ghrelin and insulin in their study (Poykko *et al.* 2003). Al Qarni *et al.* have reported that ghrelin level was reduced in Saudi patients with T2DM disease (Al Qarni *et al.* 2017).

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

(1) Insulin level was decreased in the serum of T1DM women, but increased in the serum of T2DM women.

(2) leptin levels was increased in the serum of women with T1DM, and women with T2DM, compared to their corresponding control women.

(3) Glucose and HbA1c levels were increased significantly in women with T1DM, and women with T2DM.

(4) The items of lipid profile were changed significantly in T2DM women, but did not differ in women with T1DM.

(5) Women with T1DM and women with T2DM have shown significant higher levels of CRP.

(6) The level of ghrelin was decreased in the serum of women with T1DM, and women with T2DM.

(7) Leptin has correlated positive with insulin in women with T2DM.

(8) Ghrelin has shown significant negative correlation with BMI in women with T2DM.

5.2 Recommendations

(1) The good control of glycemia is highly recommended in patients with T1DM and T2DM.

(2) Regulating leptin and hepcidin may improve the glycemic control of diabetic patients of both types.

(3) Future study on the relationship of resistin and interferon gamma in patients with T1DM and T2DM.

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CURRICULUM VITAE

Personal Information

Name and Surname : Hajir Adnan Dahham MAAMER

Education

MSc	Çankırı Karatekin University Graduate School of Natural and Applied Sciences Department of Chemistry	2021-2023
Undergraduate	Baghdad University Faculty of sciences for girls Department of Chemistry	2014-2018