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EVALUATION THE ROLE OF INTERLEUKIN-17 AND INTERLEUKIN 37 IN PATHOGENESIS OF TYPE-2 DIABETES

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AHMED MOHAMMED ALI ALI

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EVALUATION THE ROLE OF INTERLEUKIN-17 AND INTERLEUKIN 37 IN PATHOGENESIS OF TYPE-2 DIABETES

By Ahmed Mohammed Ali ALI

February 2022

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

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ABSTRACT

EVALUATION THE ROLE OF INTERLEUKIN-17 AND INTERLEUKIN 37 IN PATHOGENESIS OF TYPE-2 DIABETES

Ahmed Mohammed Ali ALI

Master of Science in Chemistry

Advisor: Assoc. Prof. Dr. Şevki ADEM

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February 2022

Diabetes is a serious non-communicable disease of two types of different pathophysiology. Since they cause a great impact on health, thus no effort is spared in investigating the risk factors of the disease. In this thesis was aimed to determine the correlations between diabetes and interleukins (17 and 37). 140 persons from Al-Jamhoury general hospital in Kirkuk in Iraq were randomly selected, were 70 of them had the disease and another 70 were free of the disease, 35 of each group were females and 35 of them were males, after ethical approval. Each blood samples were investigated for vitamin D level, blood urea level, serum creatinine, lipid profile test (cholesterol, triglycerides, high-density lipoprotein ,and low-density lipoprotein) in addition to patients' glycemic status (fasting blood glucose and hemoglobin A1C) and interleukins 17 and 37. Results showed that interleukin 17 and 37 were found to be significantly higher in the patients' group and were correlated with fasting blood sugar and hemoglobin A1C with a negative correlation with both age and body mass index. It also determined the glycemic status to be negatively correlated with age, weight, vitamin D, blood urea ,and dyslipidemia.

2022, 35 pages

Keywords: Interleukin-17, Interleukin-37, Diabetes, Lipid profile, Vitamin D

ÖZET

TİP-2 DİYABET PATOJENİZİNDE INTERLEUKİN-17 VE INTERLEUKİN 37'NİN ROLÜ DEĞERLENDİRİLMESİ

Ahmed Mohammed Ali ALI

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Şubat 2022

Diyabet, iki tip farklı patofizyolojiye sahip ciddi, bulaşıcı olmayan bir hastalıktır. Sağlık üzerinde büyük bir etkiye neden olduklarından, hastalığın risk faktörlerinin araştırılmasında hiçbir çabadan kaçınılmamaktadır. Bu tezde diyabet ile interlökinler(17 ve 18) arasındaki ilişkilerin belirlenmesi amaçlanmıştır. Irak'ın Kerkük kentindeki Al-Jamhoury genel hastanesinden rastgele seçilmiş, 70'i hastalıklı, 70'i hastalıksız, her gruptan 35'i kadın ve 35'i erkek olmak üzere etik onay alındıktan sonra 140 kişi rastgele seçilmiştir. Her kan örneğinde hastaların glisemik durumuna (açlık kan şekeri ve hemoglobin A1C) ek olarak D vitamini düzeyi, kan üre düzeyi, serum kreatinin, lipid profil testi (kolesterol, trigliseritler, yüksek yoğunluklu lipoprotein ve düşük yoğunluklu lipoprotein) ve interlökinler 17 ve 37 araştırıldı. Sonuçlar, interlökin 17 ve 37'nin hasta grubunda anlamlı olarak daha yüksek olduğunu, hem yaş hem de vücut kitle indeksi ile negatif bir korelasyona sahip olan açlık kan şekeri ve hemoglobin A1C ile ilişkili olduğunu gösterdi. Ayrıca, glisemik durumun yaş, kilo, D vitamini, kan üresi ve dislipidemi ile negatif korelasyon gösterdiğini belirlendi.

2022, 35 sayfa

Anahtar Kelimeler: İnterlökin-17, İnterlökin-37, Şeker hastalığı, Lipit profili, D vitamini

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Ahmed Mohammed Ali ALI

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CONTENTS

LIST OF SYMBOLS

%	Percentage
±	Plus minus
C	Degree Celsius
dL	Deciliter
g	Gram
kg	Kilogram
L	Liter
mg	Milligram
mL	Milliliter
mmol	Millimole
ng	Nanogram
pg	Picogram

LIST OF ABBREVIATIONS

CRP	C reactive protein
DM	Diabetes mellitus
IL	Interleukin
STAT	Signal transducer and activator of transcription
Th	T helper cells
TNF	Tissue necrosis factor
UAE	Urinary albumin excretion
UV	Ultra violet

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1. INTRODUCTION

Diabetes is a non-communicable serious health problem that has a great impact on the health care system. It is of two types: Type 1 diabetes, also known as juvenile or insulin-dependent diabetes, is caused by an autoimmune loss of pancreatic beta cells. Type 2 diabetes is caused by a reduction in tissue insulin sensitivity, thus requiring a larger amount of insulin to meet the level of euglycemia, this increase in insulin production causes the exhaustion of the pancreatic beta cells and the inability to secrete the required amount of insulin, and eventually leading to hyperglycemia and diabetes mellitus (Monesi *et al.* 2012). It has an increasing effect on the personal and governmental economy to treat elevated blood glucose and its associated complications, which was estimated by the American Diabetic Association to be over 327 billion dollars in 2017. Insulin sensitivity and glucose tolerance are influenced by many factors. The most valued of which are lifestyle variables, which are recognized to have an essential role in illness progression, Raised consumption of saturated fats and trans-fatty acids in the diet significantly increased the risk of diabetes. Obesity was discovered to be a factor in around 55% of type 2 diabetes patients (Brooks 2009). This relation was suggested to be due to the chemical signals sent by adipose tissue (especially by the visceral fat) (Shoelson *et al.* 2006). One of the risk variables evaluated was sleep disruptions, which might be the reason for increased diabetes incidence in industrialized countries due to fewer hours of sleep and to a more stressful lifestyle (Knutson *et al.* 2007).

Diabetes can cause a variety of distressing complications and increase the risk of premature mortality, it also causes great damage to blood vessels and nerves thus causing heart attacks, strokes, kidney failure, diabetic foot (gangrene), vision loss among other complications (Harding *et al.* 2019). To help prevent the start or progression of type 2 diabetes, lifestyle modifications such as regular exercise, a good diet, and quitting smoking were suggested, as well as managing underlying medical disorders such as hypertension and dyslipidemia. After the development of the disease, patients should take steps to decrease the progression of complications by achieving a

euglycemic level either by lifestyle alone or by combining it with pills or insulin injection, according to the patient's condition (Who 2016).

Recently, mild inflammation has been linked to the development of this disease in studies. Inflammatory markers and cytokines like the interleukins were found to be either elevated IL17 or suggested to have a protective effect on IL37. Interleukins are cytokines that are generated by a variety of cells, including leukocytes, in response to antigens and infections, and they play a critical role in the inflammatory response. They are made up of a huge number of proteins that initiate a sequence of reactions. They may have a paracrine effect on nearby cells or an autocrine effect on the cell itself (Akdis *et al.* 2011). T helper 17 produces IL17 as a proinflammatory cytokine in response to interleukin 23, and it is greater in females than men in a variety of immune-related illnesses including rheumatoid arthritis, asthma, lupus, and allograft rejection (Aggarwal *et al.* 2002). While IL37 has an anti-inflammatory effect and helps to regulate innate immunity, immune cells such as B lymphocytes, natural killer cells, and monocytes make it, it was found to be elevated in lupus patients, it also has an anti-cancer effect immunosuppressive and metabolic regulation effect.

The aim of this study, the correlation between interleukin-17 and interleukin-37 with diabetes and blood glucose was tested in this letter, other parameters like lipid profile and renal function test were also included. The purpose of this study is to measure accurately the concentration of IL-17, IL-37. The possible relationship between these biomarkers and diabetes severity and control will be investigated.

2. LITERATURE REVIEW

2.1 Diabetes

Diabetes is a serious chronic disease caused by the pancreas's inability to produce enough insulin (a hormone that regulates blood sugar (glucose)) or by the body's inability to utilise the insulin produced by the pancreas (Mukhtar 2020). Diabetes is a serious public health issue and one of the important diseases on which international leaders are concentrating their efforts. Diabetes has been on the rise over the last few decades, both in terms of the number of cases and the prevalence of the disease (Monesi *et al.* 2012).

2.1.1 Pathophysiology

There are mainly three types of diabetes each having distinct pathophysiology, but they all share similar symptoms and complications (Baynes 2015). Type two diabetes is the focus of this study.

2.1.2 Type one diabetes

In type one diabetes, the pancreatic beta cells are attacked by the immune system, destroying them, and reducing insulin production. Total insulin insufficiency is the result of this damage. Anti-insulin or anti-islet cell antibodies in the blood might be the cause of an autoimmune illness. Infiltration of lymphocytes and loss of pancreatic islets follow. Type 1 diabetes symptoms might appear in a matter of days to weeks, even though this process takes months to develop. Hypothyroidism and vitiligo are two other autoimmune disorders connected to type 1 diabetes. Insulin therapy is always necessary for type 1 diabetic patients who do not react to oral insulin-stimulating medications.

2.1.3 Type two diabetes

When the body's insulin production isn't enough to fulfill the body's demands diabetes type 2 develops. Additionally, to insulin resistance in the peripheral, which is characterized as high insulin levels in the blood without hypoglycemia, beta-cell insufficiency exists. It could be due to differences in insulin receptors that regulate the actions of insulin, resulting in a cascade of metabolic events (Figure 2.1).

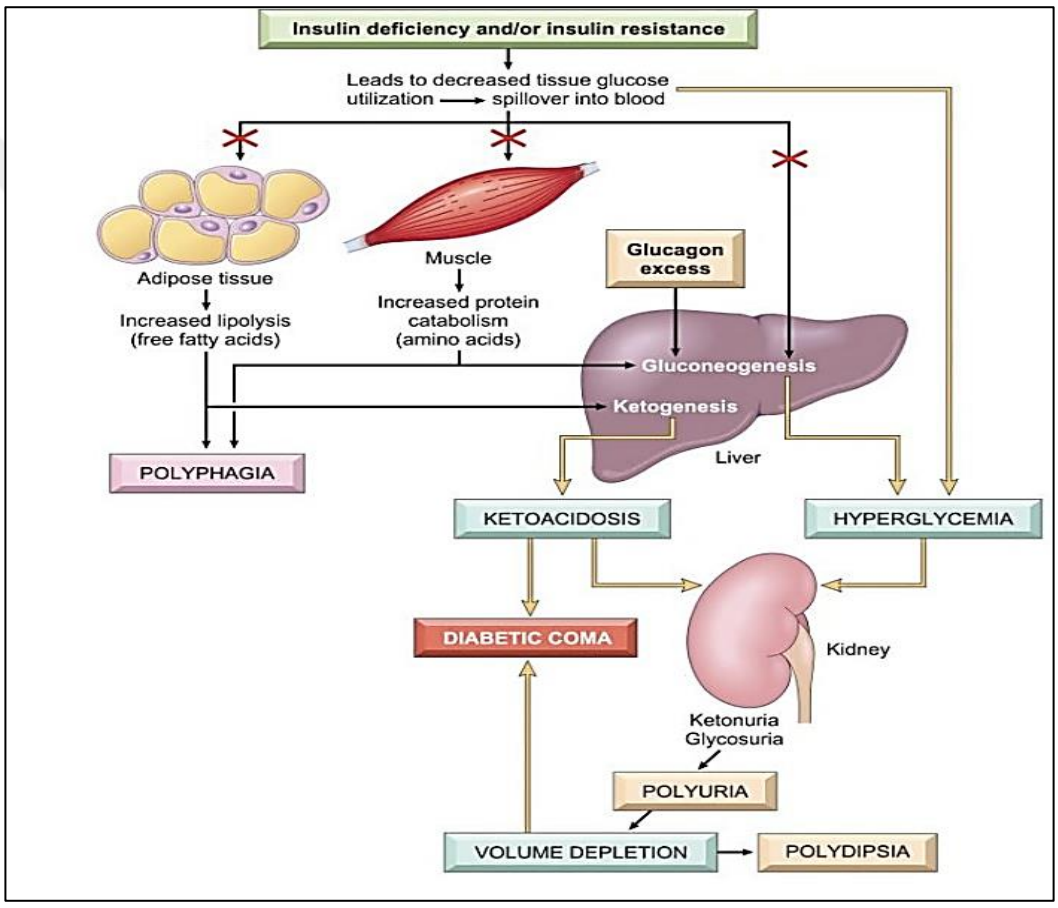

Figure 2.1 Metabolic derangement sequence underlying the clinical manifestation of diabetes

When oral medications fail to induce enough insulin release, most type 2 diabetics will become insulin-dependent. Elevated blood glucose is caused by a discrepancy between the amount of insulin required and the amount available. This imbalance can be caused by relative insulin insufficiency, target tissue insulin resistance, or both.

Insulin resistance causes the liver to fail to suppress endogenous glucose synthesis. After meals, it also reduces glucose absorption and glycogen formation in skeletal muscles. Furthermore, in adipose tissues, it fails to block hormone-sensitive lipase activity. Beta-cell mass and function, receptors and proinsulin, glucagon synthesis, glucose production in the liver, and how cells respond to insulin stimulation are all related. Epigenetic alterations that occur across generations in response to environmental stimuli cause genetic disorders. Type 2 diabetes is thus induced by a mix of inherited, epigenetic, and environmental variables. While many people are insulin resistant and at risk for type 2 diabetes, only those who are genetically predisposed to beta-cell malfunction will succumb to the condition. Insulin resistance is produced by abnormal insulin molecules, an excess of insulin antagonists, insulin receptor down-regulation, reduced or improper activation of post-receptor kinases, and alterations in glucose transporter proteins. Obesity plays a significant impact on insulin resistance (Figure 2.2).

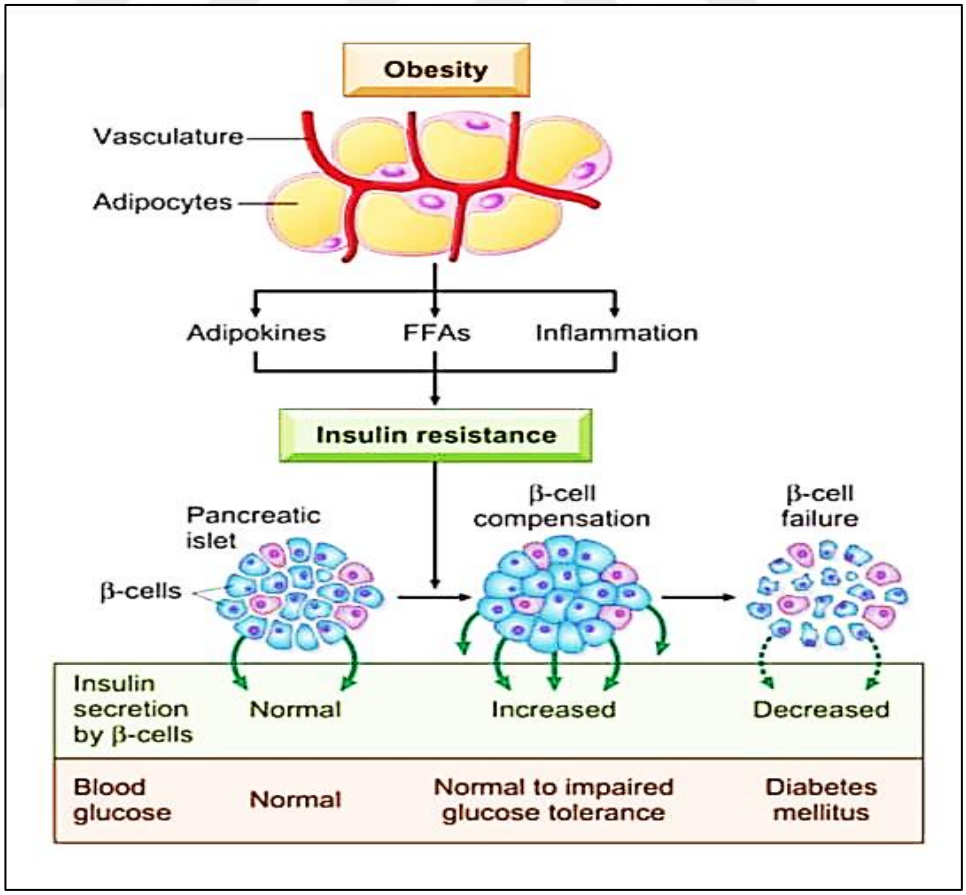

Figure 2.2 Development of type two diabetes 1

Beta-cell decrement in function is caused in part by a reduction in beta-cell mass, which is especially susceptible to high glucose levels and may result in apoptosis. Dysfunction can also be caused by an inflammatory reaction and changes to adipokines. Furthermore, numerous inflammatory cytokines are harmful to beta cells. Aside from its impact on insulin resistance, adipose tissue raises FFA levels in the blood, It has been found that exhibits endocrine activities and can block insulin-stimulated glucose transport and glycogen synthase activity in muscular adipose tissue. By producing adipocytokines that might be advantageous to metabolism (adiponectin) of frequently unfavorable (IL-6, leptin, resistin, and TNF).

2.1.4 Global burden

In 2014, 422 million people worldwide were estimated to have diabetes, up from 108 million in 1980. Diabetes has nearly doubled in global prevalence, It has risen from 4.7 percent to 8.5 percent in the last forty years (age-standardized). This indicates that risk factors including being overweight or obese have become more prevalent. During the recent decade, diabetes prevalence has increased faster in low- and middle-income countries than in high-income countries. In 2012, 1.5 million individuals died as a result of diabetes. A higher-than-optimal blood sugar level increased the risk of cardiovascular disease and other ailments, resulting in an additional 2.2 million deaths. Under the age of 70, 43 percent of the 3.7 million persons died. The percentage of deaths caused by high blood glucose or diabetes before the age of 70 is higher in low- and middle-income countries than in high-income countries (WHO 2016). There are no isolated estimates on the prevalence of diabetes type 1 and type 2 because extensive laboratory tests are usually necessary to distinguish between type 1 diabetes (which requires insulin injections to survive) and type 2 diabetes (in which the body's insulin is not being utilised effectively). The vast majority of diabetics have type 2 diabetes. This used to be mostly an issue for adults, but it is increasingly affecting the young as well.

2.1.5 Complications

Diabetes, in any form, can cause difficulties in a variety of body organs and increase the chance of dying early. It also makes a great economic effect on people with the disease and their families, and the economy of the health systems and national economies, along with its complications (Harding *et al.* 2019).

2.1.6 Cardiovascular diseases

Cardiovascular disease is the greatest cause of mortality and disability among diabetic individuals. As the number of individuals diagnosed with diabetes climbs, so will the number of people diagnosed with cardiovascular disease. When compared to people without diabetes, Diabetes increases the chance of hospitalization for serious cardiovascular disease and cardiovascular disease-related clinical procedures by a factor of two to four (Cho *et al.* 2018).

2.1.7 Lower extremity amputation

Because of the physical, economic, and psychosocial consequences, lower extremity amputations are one of the most serious complications for adults with diabetes. Because several etiological pathways are linked to conditions that result in lower extremity amputations, they are also a good predictor of how well preventive care, such as glycemic control, Management of risk factors for cardiovascular disease, as well as the diagnosis and treatment of those who are at high risk of developing foot injuries are working. Between 1982 and 2011, there was a 3 percent to 85 percent decline in the rate of lower extremity amputations across diverse demographics, according to studies (Narres *et al.* 2017).

2.1.8 Diabetic nephropathy

Diabetes and hypertension are estimated to be the root causes of more than 80% of end-stage renal disease cases worldwide. Diabetic nephropathy is the most common cause of

kidney damage in persons starting renal replacement treatment, affecting around 40% of type 1 and type 2 diabetics. It increases the danger of death, which is primarily due to cardiovascular reasons (Gross *et al.* 2005). Diabetic retinopathy is the most frequent diabetes-related illness. It has long been recognized that it is a microvascular condition. The discovery of microvascular lesions is required for the diagnosis of this condition. In addition to microvascular alterations, laboratory and clinical investigations have shown that inflammation and retinal neurodegeneration may have a role in diabetic damage of the retina in the early phases of diabetic retinopathy. More research into the disease's molecular causes could lead to the development of new early-intervention strategies (Wang *et al.* 2018).

2.1.9 Other complications

Neuropathy and acute difficulties like hypoglycemia and diabetic ketoacidosis are further major effects that place a strain on both the patient and the healthcare system (Duca *et al.* 2017).

2.2 Laboratory Biochemical Test

2.2.1 Interleukins

Interleukins (IL) are cytokines that were once thought to be generated solely by white blood cells, now it has been shown that several different bodily cells make these cells. Immune cells' activation and differentiation, as well as their proliferation, maturation, migration, and adhesion, are all influenced by them. Anti-inflammatory and pro-inflammatory activities are also present. Interleukins' fundamental function in the inflammatory and immunological response process is to influence growth, differentiation, and activation. Interleukins are a family of proteins that attach to high-affinity receptors on the cell surface and trigger a variety of responses in cells and tissues. They are also capable of inhibiting and limiting paracrine and autocrine action. Interleukins are also employed to investigate clinical medicine difficulties in animal studies (Akdis *et al.* 2011). Cytokines are proteins that govern, modulate inflammatory,

and immunological responses. Infections and other antigens cause them to be generated. Interleukin production is a self-contained process. Most interleukins are encoded by messenger RNA, which is unstable and ltsresu in transitory production. Once created, these compounds are easily secreted. Up- and down-regulation processes, as well as the activation and participation of genes encoding for cytokine receptor inhibitors, are all cellular responses to interleukins (Justiz *et al.* 2021). Interleukins perform several functions. B-cell growth factors, such as IL-4, IL-13, and IL-5, promote B-cell development. B cells change antibody isotypes in response to cytokines, helper T cells develop into Th-1 and Th-2 subgroups, and phagocytes participate in microbicidal operations. Interleukins frequently influence the production and effects of other interleukins. IL-1, for example, increases lymphocyte activation, which results in the production of IL-2. External signals or receptors with a high affinity for cytokines activate and regulate cytokine responses in cells. When infections stimulate B-cells, the expression of cytokine receptors increases. Cytokines can either act on the same cell that secretes the cytokine (for example, IL-2 released by T cells hits the same T cells that produced it or a neighboring cell) or they can reach the bloodstream and act on cells that are not the source of the cytokine. (For example, IL-1 is an internal pyrogen that affects the central nervous system and produces an increase in the temperature), or cytokines can enter the circulation and operate in a different location. Interferon-gamma and interleukin-2 have both been used successfully in the immunotherapy of renal cancer and melanoma. The way by which they function is by the activation of natural killer (NK) cells and T lymphocytes. These two cytokines have FDA authorization for use in the treatment of these two cancers. There are more than 40 different interleukins, each with a unique purpose and effect on cells; the ones discussed in this letter are IL-17 and IL-37, as well as their impact on diabetes mellitus (Justiz *et al.* 2021).

2.2.2 Interleukin 17

The interleukin 17 cytokine family includes a pro-inflammatory cystine knot known as interleukin 17. T helper 17 (Th17) cells, a subpopulation of T helper cells, produced them in response to IL 23 stimulatio (Moseley *et al.* 2003). Both endothelial and epithelial cells are affected by this. The release of IL6 and other pro-inflammatory

cytokines is one of IL17's main activities. It improves antigen-presenting cell function. As a result, endothelial cells are stimulated to create chemokines (Dhaouadi *et al.* 2018). IL17 A through F is the members of the IL17 family in humans. IL17E is also known as IL25. The protein structure of all members of the IL17 family is similar. Their protein sequences contain 4 cysteine residues that are exceedingly conserved. The proper three-dimensional form of the entire protein molecule depends on these conserved cysteine residues (Kolls *et al.* 2004).

Cytokine production has several effects, including airway remodeling, which is a characteristic of IL17 responses. Chemokine expression is increased, which attracts other cells such as neutrophils. T helper 17 (Th17) cells are an important role in IL17. The IL17 family has been related to several immune/autoimmune illnesses, including asthma, allograft rejection, rheumatoid arthritis, lupus, anti-tumor immunity, and more recently psoriasis, multiple sclerosis, and intracerebral hemorrhage, due to these functions. (Aggarwal *et al.* 2002, Zhu *et al.* 2019) (Figure2.3).

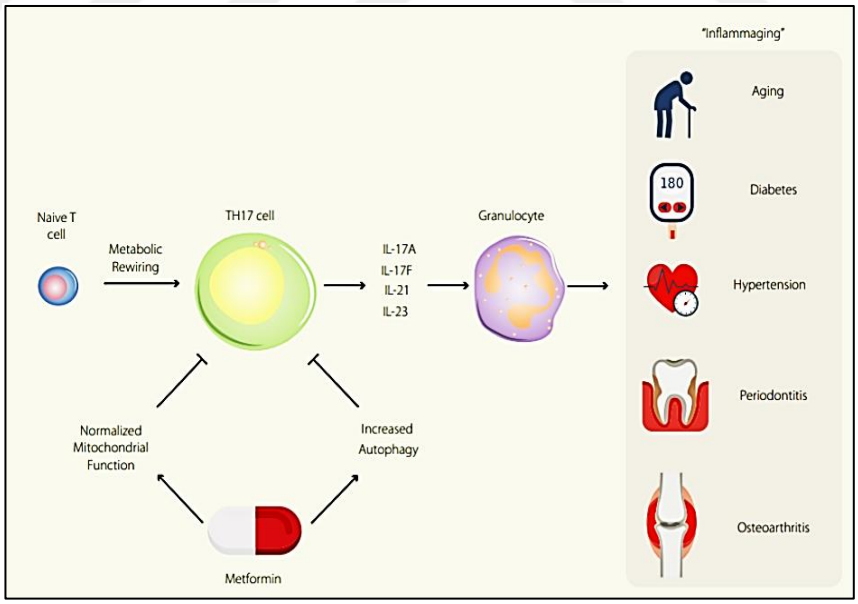

Figure 2.3 Naive T cells evolved into T helper 17 (Th17) cells and their metabolic effect (Chang *et al.* 2021)

According to one study, IL-17 levels were substantially greater in females than in males, Insulin resistance, insulin, BMI, waist circumference, fasting blood sugar, and

age were all connected to it. These associations, on the other hand, were moderate (Zareian *et al.* 2014).

2.2.3 Interleukin 37

The anti-inflammatory cytokine Interleukin 37 (IL-1F7) belongs to the IL-1 family of cytokines (Wang *et al.* 2018). In humans, the IL-37 gene is located on the long arm of chromosome 2. IL-37 has five distinct splice variants, ranging from IL-37a to IL-37e. The largest and most investigated subfamily of the interleukin-1 family is IL-37b, which shares the beta-barrel shape found across the interleukin-1 family.

Interleukin-37 is involved in the control of innate immunity, which leads to immunosuppression. This enzyme is found in phagocytes and organs such as the testis, uterus, and thymus. In autoimmune illnesses, IL-37 regulates the immune system and the inflammatory response. Mucocutaneous and renal involvement were connected to high disease activity, and IL-37 levels were greater in lupus patients than in healthy controls (Akdis *et al.* 2011). IL-37 a, b, and c are found in a vast range of tissues, including the colon, thymus, bone marrow, lung and uterus. Immune cells such as activated B lymphocytes, monocytes, and natural killer cells generate it, although epithelial cells and keratinocytes also make it. Some isoforms of IL-37 are present in particular tissues, such as the brain, whereas IL-37b is found in the skin, bone marrow, kidney, blood, urogenital tract, and respiratory system. IL-37c is specialized for cardiac tissue, while IL-37d is specific for the testis and bone marrow (Wang *et al.* 2018).

Interleukin 37, like the other interleukin-1 family members, is produced as a precursor before being fully activated by caspase 1. Caspase is an Interleukin-1 conversion enzyme that proteolytically cleaves and converts other proteins to their active forms, such as interleukin 1 and interleukin 18 (precursors of inflammatory cytokines). In addition to these interleukins, it is an important inflammatory response initiator in cell immunity. It is activated by the creation of an inflammasome complex, which subsequently triggers a pro-inflammatory response by cleaving and activating the inflammatory cytokines interleukin 1 (IL-1) and interleukin 18 (IL-18), as well as

pyroptosis, a kind of programmed cell death, by cleaving Gasdermin D (Xia *et al.* 2021). Caspase-1 triggered cytokines are ejected from the cell, causing additional inflammation in adjacent cells. IL-37 possesses remarkable anti-inflammatory properties, in addition to that, it may be significantly effective as anticancer, immune deviatory, immunosuppressive, and regulation of metabolic activity. IL-37 significantly reduces cytokine release in dendritic cells, and macrophages, in addition to inhibiting their activation and differentiation. IL-37 is extensively expressed in numerous cancer cells, in addition to healthy tissues. The recruitment of NK cells into tumor tissues by IL-37 generates an anticancer immune response. STAT-3 is activated when IL-37 binds to its receptor, but NF-kB signals are inhibited (Figure 2.4).

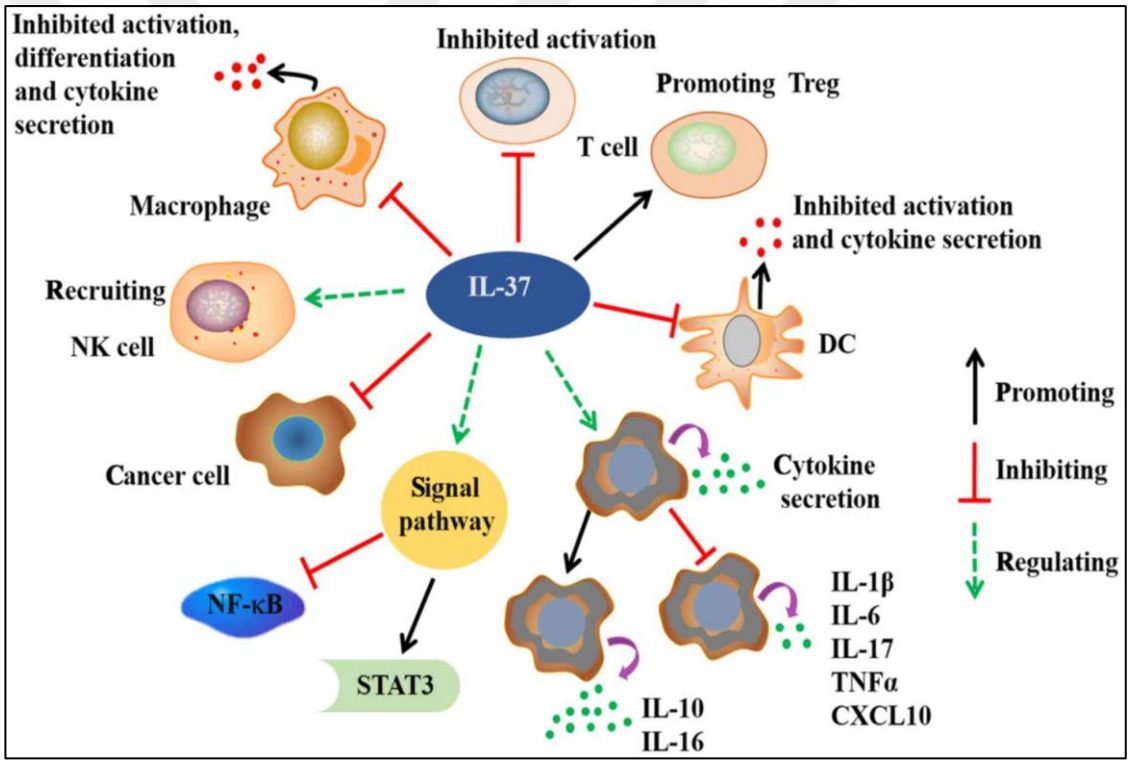

Figure 2.4 Possible biological functions of IL-37 (Wang *et al.* 2018)

Caspase inhibition is by CARD only proteins (COP) thereby inhibiting the activity of associated interleukins (Jorgensen and Miao 2015).

2.2.4 Interleukins and diabetes

Obesity and insulin resistance have been linked to a systemic, low-grade inflammatory process in adipose tissue recently. Multiple studies have discovered an association between cancerous growth and systemic chronic inflammation, changes in cytokine synthesis and activation of inflammatory signaling pathways characterize this condition. Inflammatory cytokines such tumor necrosis factor (TNF), interleukins (ILs), and cytokine-related proteins are thought to play a role in the development of insulin resistance (adipokines). Some of the compounds listed above are thought to be released by adipocytes, whereas others, such as macrophages, are primarily generated by the stromal vascular fraction's cells (Fain *et al.* 2004).

Interleukins' impacts on insulin signaling pathways and -cell activity are most likely involved in the development of insulin resistance and type 2 diabetic mellitus. Two interleukin systems, in this setting significant, are IL-6 and the IL-1-IL-6 balance are its receptor antagonist. IL-1 and IL-1 modify insulin signaling pathways by lowering the expression of various components of glucose transport that is regulated by insulin and changing the phosphorylation of insulin-receptor substrates. In insulin resistance, IL-6 is produced in greater ratios and affects the action of insulin in the liver and the adipose tissue, these roles are connected to the concentration and duration of IL-6 exposure in target tissues (Fève and Bastard 2009). The relationship between interleukin-17 and interleukin-37 and diabetes type 2 is studied in this letter. Interleukin-17 has been linked to the pathophysiology of atherosclerosis (Cheng *et al.* 2008, Smith *et al.* 2010). Adipocyte differentiation and glucose metabolism are also involved, through the production of low-grade inflammation. IL-17 also influences immune responses by increasing the production of proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF-), both of which are connected to the development of insulin resistance (Aggarwal and Gurney 2002). Patients who were older (De Angulo *et al.* 2015) or had diabetes (Chen *et al.* 2016, Zareian *et al.* 2014, Qiu *et al.* 2021) showed significantly higher induction of Th17 cells, IL17 levels, or IL17 tissue expression compared to young or nondiabetic patients.

Interleukin-37 is a recently discovered cytokine that inhibits innate and acquired immunity reducing tissue damage caused by autoimmune and inflammatory diseases by binding to the IL-18 receptor alpha chain (Quirk and Agrawal 2014). It also reduces cellular differentiation and proliferation by inhibiting cytokine levels such as IL-18, IL-33, IL-1, TNF, and IL-6, with protective benefits in animal models (Dinarello and Bufler 2013).

IL-37 is an anti-inflammatory medication that can help with beta-cell function, heart attacks, inflammation, and oxidative stress (Ballak *et al.* 2014). Inflammatory cytokines and C reactive protein levels are reduced (CRP), Hepatocytes manufacture it in response to inflammatory cytokines including IL-1, IL-18, and IL-6, interleukin-37, in combination with other effective treatments, may help T2DM patients avoid cardiovascular events (Ballak *et al.* 2014). IL-37 reduces IL-1 activity, which can lead to significant improvements in a variety of measures, including IL-6 and CRP secretion by monocytes. In diabetics with type 2 diabetes, blocking inflammatory cytokines generated by monocyte activity may reduce the risk of significant consequences such as stroke, myocardial infarction, and systemic inflammation (Dinarello and Bufler 2013). Antigen-stimulated monocytes secrete inflammatory mediators like cytochemokines and chemical mediators, which may influence macrophages and cause them to create IL37, an anti-inflammatory molecule. IL-37 prevents monocytes from becoming activated, IL-33, MC-IL-1, TNF, and IL-6, in type 2 diabetes, which has a favorable effect on low-grade inflammation. This suppression may help type 2 diabetic patients improve their clinical and pathological problems. IL-37 has anti-inflammatory effects, suppresses macrophage activation, and lowers leukocyte adhesion, among other things. IL-37 has been studied for its therapeutic effects in inflammatory diseases by numerous authors, who found that it reduced disease severity and improved patient quality of life. The action of IL-37 is most likely related to a drop in myeloid differentiation factor 88.and/or activation of anti-inflammatory inhibitors such as IL-10, tissue growth factor, and IL-1Ra (Ballak *et al.* 2014). The IL-18R-alpha chain regulates and blocks the activity of members of the IL-1 family. By binding to IL-37, it may be employed in clinical practice to treat a range of inflammatory illnesses, including type 2 diabetes.

For a long time now, Diabetes and its complications have been addressed with diet, drugs, and injections, with varying levels of success; nevertheless, in conjunction with known medicines, therapy with this new cytokine, IL-37, may enhance patients' health. By influencing the gastrointestinal system, the medicine not only decreases inflammation but also has the potential to improve glucose metabolism, which produces hormones that have a profound impact on diabetes. By inhibiting the macrophage response and preventing their accumulation, IL-37 decreases insulin resistance and inflammation. Treatment with IL-37 may reduce the risk of complications associated with type 2 diabetes, such as heart attack, mortality, and stroke. An IL-37 blocking drug was indicated to enhance the pathophysiology of cardiovascular health and diabetes, according to a new paradigm of prevention and cure for inflammatory illnesses even if a strong inhibitor might make you more susceptible to illnesses. It is still possible to employ IL-37 as a therapeutic agent to improve physiologic parameters in inflammatory diseases. Nonetheless, the treatment of patients with IL-37 must be carefully considered, as it is a cytokine with substantial side effects, including high toxicity that can result in death (Ballak *et al.* 2014).

2.2.5 Other parameters

Vitamin D levels were also measured in this study due to its suggested effect on diabetes and diabetic complications (Bilir *et al.* 2016, Zemunik *et al.* 2005). Lipid profile abnormalities facilitate abnormal inflammation processes that can be contributed to beta cells' function and insulin resistance (Shoelson *et al.* 2006). Interleukins were discovered to have a function in the progression of diabetic renal problems, thus a renal function test was also done in this study (Kim *et al.* 2012).

Vitamin D and diabetes: The first indication of a link between vitamin D and type 2 diabetes in humans came from a study that found both healthy and diabetic people exhibited seasonal glycemic control changes. These statements are now backed up by evidence indicating vitamin D deficiency is required to manage particular pathways linked to the development of type 2 diabetes. Because activation of inflammatory pathways compromises normal metabolism and changes insulin signaling, vitamin D

may alter glucose homeostasis by influencing the inflammatory response. There have been limited and inconsistent studies on the effect of vitamin D supplementation on inflammatory biomarkers in persons with type 2 diabetes. Vitamin D's beneficial effect seems to be mostly due to its effects on insulin production and tolerance, with a side benefit on bone health (Zareian 2014).

Vitamin D deficiency may be linked to impaired glucose tolerance. Reduced insulin production has been related to type 2 diabetes, according to a new study (Pittas *et al.* 2010, Thorand *et al.* 2011). This might be due to vitamin D receptors being directly activated or a second effect on calcemic hormones and inflammation.

Insulin synthesis and release are both dependent on vitamin D. Because pancreatic cells contain both vitamin D receptors and 1-hydroxylase (Pittas *et al.* 2010). Based on epidemiological studies, vitamin D supplements are recognized as a realistic and cost-effective treatment for preventing the progression of type 2 diabetes and the improvement of glycemic indices in type 2 diabetics (Takiishi *et al.* 2010), whereas other studies revealed no effect on glucose tolerance (Pittas *et al.* 2007).

Lipid profile: Inflammation in the adipose tissue is connected to both glucose intolerance and insulin resistance (Osborn *et al.* 2012). Inflammatory responses are induced in adipose tissue, skeletal muscle, the liver, the pancreas, and the hypothalamus as a result of dietary excess, leading to insulin resistance and glucose intolerance in the body (Osborn *et al.* 2012).

Macrophage infiltration, which can account for up to 40% of adipose tissue cells, and Insulin resistance, glucose tolerance, and metabolic syndrome have all been linked to it, and type 2 diabetes, is a hallmark of adipose tissue inflammation. TNF and interleukin 1 are paracrine cytokines that can have a local effect, or they can be expelled from adipose tissue, causing systemic effects (endocrine activities). Insulin sensitivity in insulin target cells is impaired as a result (adipocytes, myocytes, and hepatocytes) (Olefsky and Glass 2010). As proinflammatory macrophages enter fat cells, they produce special chemokines, stimulating more macrophages to migrate and triggering a

positive feedback inflammatory response. Insulin resistance has been linked to proinflammatory macrophages in several investigations.

3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Sample collection

Blood was drawn in a sterilized environment and placed in separate tubes for each parameter to be tested.

3.1.2 Biochemical parameters

Vitamin D measurement (code 82306): The rivalry between vitamin D and a vitamin D tracer for a monoclonal antibody binding site is the basis for this test concept. As a result, the amount of tracer that can attach to the antibody is inversely proportional to vitamin D levels. At 412 nm, the product is extremely absorbable and has a yellow tint. A 50-liter sample of freshly obtained blood was maintained in hermetically sealed glass vials for analysis. Reagents were diluted and mixed with the sample for 5-10 minutes before and during usage. Where B is corrected counts/minutes for each tube, and B0 is corrected counts/minutes for 0 standards.

Urea measurement (code 80048): Urease hydrolyzes urea to create ammonia and carbon dioxide, and glutamate dehydrogenase converts oxoglutarate to glutamate in the presence of NADH and oxoglutarate (GlDH). At 340 nm, the rate of reduction in absorbance induced by NADH to NAD+ oxidation is kinetically monitored and is proportional to the quantity of urea present in the sample. 10 liters of serum are mixed with 1 ml of working reagent at 37 degrees Celsius with the photometer adjusted to 0 absorbances with distilled water. 4 mL Buffered Urease/GlDH (TRIS buffer mmol/L, 2-oxoglutarate, urease, glutamate dehydrogenase, Biocides). 1 mL NADH 1.50 mmol/L coenzyme. They were gently mixed by inversion before being introduced into the cell holder, where the absorbance at 340 nm was recorded after 30 seconds for A1 and 90 seconds for A2, with the difference calculated as Equation (3.1):

$$\frac{(A1\text{-}A2)_{sample}}{(A1\text{-}A2)_{standard}} \text{ X C standard} = \frac{mg}{dL} \quad (3.1)$$

Serum creatinine measurement (REF 82565): This approach works based on a modified picrate reaction. Creatinine combines with picrate ions to generate a crimson complex in alkaline circumstances. The rate of complex formation, as assessed by rising absorbance during a preset time interval, where is equal to the amount of creatinine in the sample. A 100 mL sample was pipetted into a cuvette with 1 mL of working reagent made up of 1:1 volume Picric acids (25 mmol/l) and an alkaline buffer (300 mmol/L phosphate buffer, pH 12.7, SDS 2.0 g/L), all materials were kept at 37 °C, after setting the photometer to 0 absorbances by distilled water, the sample was gently mixed with the working reagent, and a cuvette was The following is the formula for calculating the result in Equation (3.2):

$$\frac{(A2\text{-}A1)_{sample}}{(A2\text{-}A1)_{standard}} \text{X C standard} = \frac{mg}{dL} \text{creatinine} \quad (3.2)$$

Total cholesterol: Cholesterol is measured enzymatically by a sequence of processes that result in the hydrolyzation of cholesteryl esters and the oxidation of cholesterol in the 3-OH group. This process causes H2O2, and the amount of H2O2 is determined using a color-producing peroxidase-catalyzed method. The absorbance is then determined at 500 nm. The amount of cholesterol present is related to the intensity of the hue. Cholesterol Reagent, Cholesterol oxidase, Sodium cholate, 4-Aminophenazone, Phenol, Peroxidase, Cholesterol esterase, PIPES buffer, Mg2+, Fatty alcohol-polyglycol ether Buffer, and unidentified stabilizers and preservatives are among the reagents used in this technique.

Triglycerides: Enzymatic triglyceride measurement entails a sequence of chemical reactions in which triglycerides are hydrolyzed to produce glycerol, which is then oxidized by glycerol oxidase to produce H2O2, which is detected as one of the reaction products at 500 nm.

PIPES buffer, Mg^{++}, Sodium cholate, ATP, 4-Aminophenazone, 4-Chlorophenol, Potassium hexacyanoferrate (II), Fatty alcohol polyglycolether, lipoprotein lipase, glycerol kinase, glycerophosphate oxidase, Peroxidase, and an unnamed preservative were among the reagents used in this procedure.

High-density lipoprotein: Levels of high-density lipoprotein (HDL) are evaluated directly in the blood. Based on the idea that under assay circumstances. The block reagents are used to render apoB-containing lipoproteins in the sample non-reactive with the enzymatic cholesterol reagent. As a result, lipoproteins carrying apoB are efficiently filtered out of the test, leaving just HDL-chol to be identified. In the presence of Mg+2, sulfated alpha-cyclodextrin forms complexes with apoB-containing lipoproteins, as well as polyethylene glycol-coupled cholesteryl esterase and cholesterol oxidase, to test HDL cholesterol.

Low-density lipoprotein: Total cholesterol, triglycerides, and HDL cholesterol measurements are used to determine low-density lipoprotein cholesterol. Where the concentration of low-density lipoprotein is equal to total cholesterol minus HDL-cholesterol minus triglycerides concentration divided All data are measured in mg/dL and multiplied by 5, where [TG]/5 is a VLDL-cholesterol estimate. A sample volume of 0.7 mL is required to allow for full clotting and clot retraction, it was kept at room temperature for 45 minutes. The samples were centrifuged for 30 minutes at 4°C at 1,500 x g. Following centrifugation, the samples were immediately placed in an ice bath and maintained at 2-4° C.

Blood glucose (REF 82947): In the presence of ATP, hexokinase transforms glucose to glucose-6-phosphate (G-6-P), laying the groundwork for blood glucose monitoring. In the presence of $NADP^{+}$, glucose-6-phosphate dehydrogenase transforms G-6-P to gluconate-6-P. Because $NADP^{+}$ is reduced to NADPH during the process, the increase in absorbance at 340 nm is measured. For this investigation, 100 liters of serum were collected, and the specimens were centrifuged within 45 minutes of collection. TRIS buffer, Mg^{+2}, ATP, NADP, HEPES buffer, hexokinase, glucose-6-phosphate dehydrogenase, and preservative make up the reagent. Following the mixing of the

sample with the reagent, the absorbance is measured, and the glucose concentration is estimated using the formula Equation (3.3):

$$\text{serum glucose } \left(\frac{\text{mg}}{\text{dL}}\right) = \frac{\text{absorbance (sample)}}{\text{absorbance (standard)}} \times 100 \quad (3.3)$$

Fasting blood glucose was measured in the study group

Interleukin 17 (REF 83520): The washing buffer was diluted to 1:20 and thoroughly mixed. The standards and samples were serially diluted at a ratio of 1:2. Based on the expected concentration of the analyte, the sample was diluted in assay diluent to the required concentration. Everything should be kept at ambient temperature (20-25 °C). After washing the wells, allowing them to dry, and After adding the sample, the samples were incubated at room temperature for at least 2 hours. The plate was rinsed four times before adding the detecting antibody. The Plate Sealer was used to cover the samples, which were incubated after that at the temperature of 37 centigrade for 2 hours. The plate was aspirated, and the dish was washed once again. Color Development Enzyme has been added to the mix. For appropriate color development, samples were incubated at room temperature (between 2 and 12 minutes) To prevent color change, The stop solution was given to each well in the amount of 100 µL. The plate was read at a wavelength of 450 nm.

Interleukin 37 (REF 83520): To eliminate clots, samples were centrifuged at 3,000 rpm for 10 minutes at 4°C. Washing Solution was given to each well in the amount of 200 µL. The plate was cleaned three times with 300 µL of Washing Solution in each well after the wells were aspirated to remove liquid. In each well, 100 µL of standard, blank, and sample were put in duplicate. For 2 hours, the dish was covered and incubated. The wells were aspirated and cleansed to remove the fluids. Per well, 100 um of diluted detection antibody was added. The plate was then aspirated and washed after being covered and incubated for 2 hours. Per well, 100 µL of diluted StreptavidinHRP was added. Covered, the plate was incubated for 30 minutes. Following another wash, each well received 100 µL of TMB or a single TMB solution. Incubate at room temperature

for optimum color development. The stop solution was injected into each well in the amount of 100 μL.

3.2 Statistical Analysis

The findings were analyzed using SPSS 23, and descriptive data were calculated using the mean and standard deviation and it was written in the formula of (mean ± standard deviation), the study of correlation was done using ANOVA one way and P-value with the level of significance being <0.05.

4. RESULTS

4.1 Design of Study

This study was aimed towards patients with diabetes mellitus type 2, it included 70 males and 70 females aged between 38 to 70 years old. Cases were divided into two groups accordıng to gender and subgroup that ıs contaın two groups. 35 cases from patients affected by DM2, 35 of which are females and a similar number of males (patients group), 35 of healthy individuals, 35 of which are females, and a similar number of males (control group). This study was conducted in Al-Jamhoury general hospital in Kirkuk-Iraq, lab work was done in associated laboratories, the study lasted from the first of June to the thirty-first of August of 2021.

4.2 Biochemical Parameters

The standard deviation and the mean value were calculated as shown in Table 4.1.

Table 4.1 The mean and standard deviation of all tested parameters

PARAMETER	CONTROL M (N=35)	CONTROL W (N=35)	PATİENTS M (N=35)	PATİENT W (N=35)	TOTAL (N=140)	P
Age (years)	46.3 ± 7.47	39.3 ± 8.39	54.4 ± 8.17	52.1 ± 6.93	48.0 ± 8.12	0.443
Weight (kg)	69.2 ± 6.33	59.4 ± 7.78	79.3 ± 7.78	71.7 ± 10.1	69.9 ± 9.55	0.031
FBS (mg/dL)	85.1 ± 7.62	88.1 ± 7.10	203.1 ± 35.3	195.4 ± 15.7	142.9 ± 59.9	0.010
HbA1c (%)	4.98 ± 0.57	5.08 ± 0.48	8.93 ± 1.04	8.61 ± 0.71	6.90 ± 2.01	0.001
B.urea (mg/dL)	35.0 ± 5.57	29.6 ± 5.20	40.5 ± 8.14	38.1 ± 7.94	35.3 ± 10.5	0.053
S.creat (mg/dL)	0.64 ± 0.19	0.77 ± 0.19	0.86 ± 0.19	0.82 ± 0.19	0.77 ± 0.21	0.068
TC (mmol/L)	165.9 ±11.5	161.9 ± 12.6	257.4 ± 17.3	270.1 ± 16.3	213.8 ± 52.3	0.021
Tg (mmol/L)	98.1 ± 15.1	93.1 ± 13.6	186.4 ± 10.4	182.2 ± 9.94	139.9 ± 46.2	0.034
HDL (mmol/L)	55.0 ± 7.3	60.1 ± 7.56	30.7 ± 3.63	33.7 ± 4.01	44.9 ± 14.1	0.017
LDL (mmol/L)	148.5 ±13.5	150.3 ± 10.8	186.5 ± 7.27	181.8 ± 8.74	166.8 ± 20.2	0.001
Vit.D (ng/mL)	34.8 ± 4.62	25.9 ± 4.15	15.9 ± 1.30	10.9 ± 0.88	21.8 ± 2.73	0.020
IL17 (pg/mL)	7.14 ± 0.56	7.99 ± 0.79	14.7 ± 1.32	15.1 ± 0.90	11.2 ± 3.80	0.030
IL37 (pg/mL)	192.4 ±13.6	173.2 ±32.9	583.2 ± 145.7	464.5± 132.9	353.2 ± 81.2	0.010

4.2.1 Correlation of ınterleukins with blood sugar

Both of the interleukins' levels (IL17 and IL37) were found to be significantly correlated with all of the other parameters (Figure 4.1, 4.2, and 4.3) including fasting blood glucose (P-value < 0.001) and that of HbA1c (P-value <0.001) as shown in Tables 4.2 and 4.3 respectively.

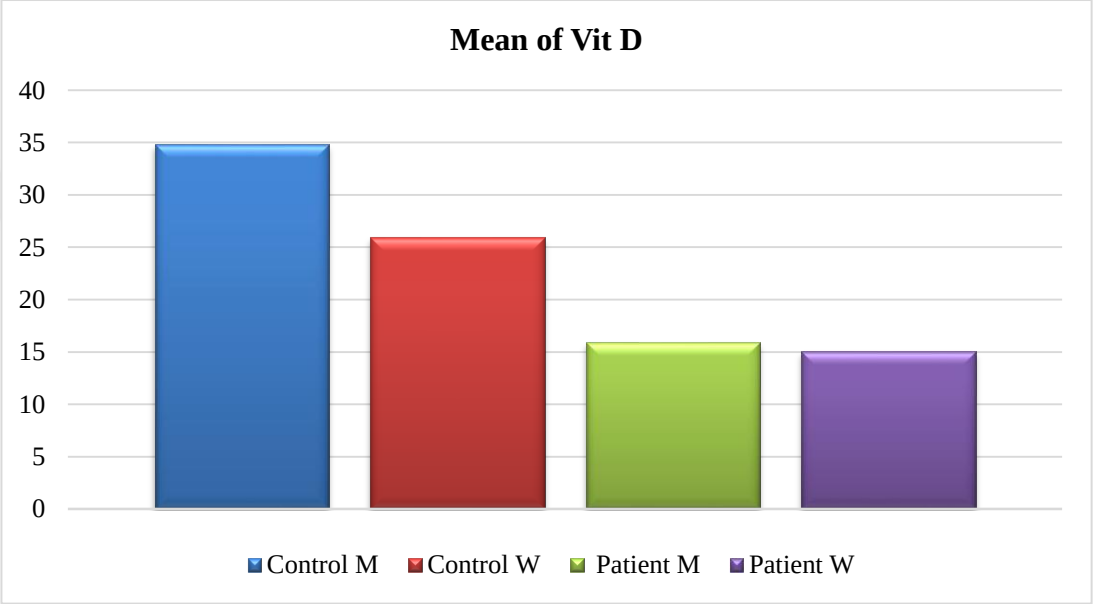

Figure 4.1 Comparison between the means of vitamin D among the groups

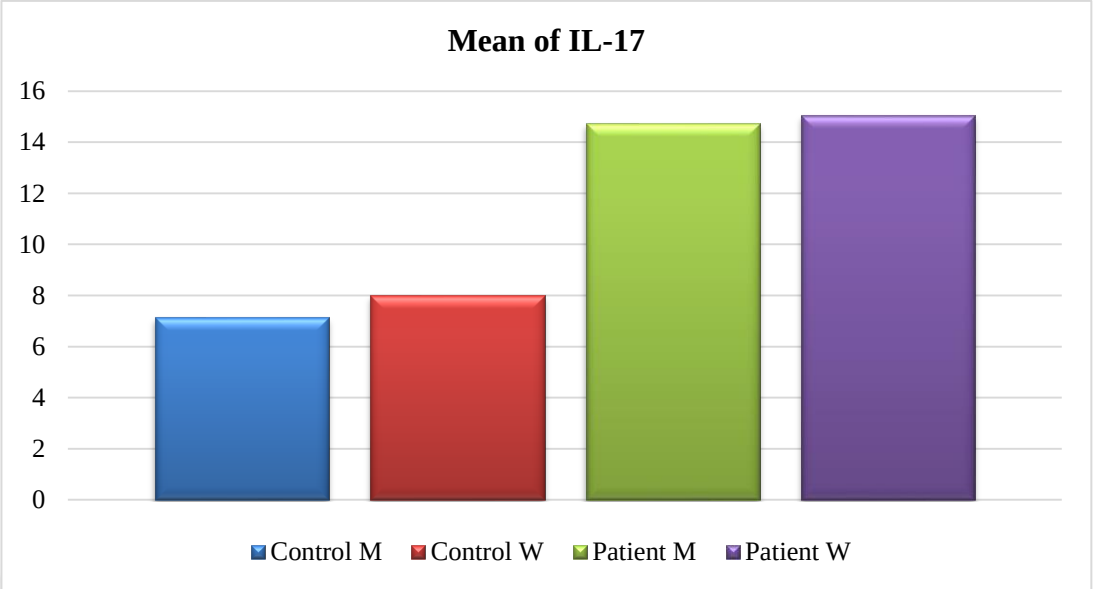

Figure 4.2 Comparison between the means of IL17 level among the groups

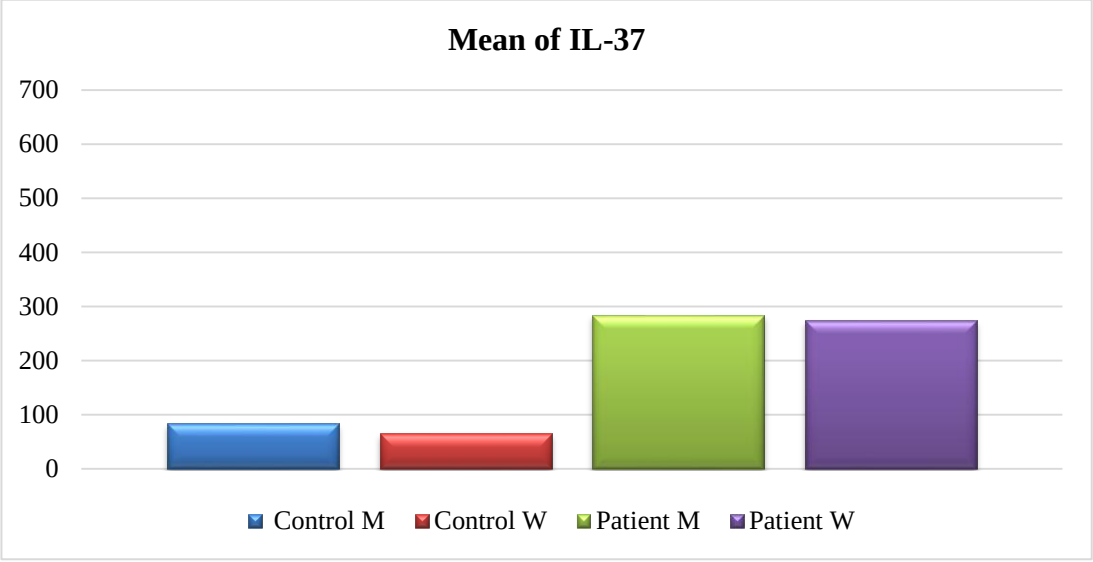

Figure 4.3 Comparison between the means of IL37 level among the groups

Table 4.2 Correlation between interleukin 17 and glycemic status

		FBS	**HBA1C**
IL17	Pearson Correlation	0.928**	0.920**
	Sig. (2-tailed)	0.000	0.000
	N	140	140

Table 4.3 Correlation between interleukin 37 and glycemic status

		FBS	HbA1c
IL37	Pearson Correlation	0.932**	0.930**
	Sig. (2-tailed)	0.000	0.000
	N	140	140

It was also found to be highly significantly correlated to all other studied parameters, where age, weight, and HDL level had a negative correlation and a positive correlation was shown with blood urea, serum creatinine, total cholesterol, triglycerides, lipid profile, and vitamin D as shown in Tables 4.4 and 4.5.

Table 4.4 Correlation of IL 17 levels with other parameters

IL17			
TESTS	**PEARSON CORRELATİON**	**SİG. (2-TAİLED)**	**N**
Age	0.323**	0.000	140
Weight	0.408**	0.000	140
B. Urea	0.755**	0.000	140
S. Creatinine	0.314**	0.000	140
Tc	0.925**	0.000	140
Tg	0.924**	0.000	140
HDL	0.856**	0.000	140
LDL	0.819**	0.000	140
Vit. D	0.942**	0.000	140

Table 4.5 Correlation of IL 37 levels with other parameters

IL37			
TESTS	**PEARSON CORRELATİON**	**SİG. (2-TAİLED)**	**N**
Age	0.234**	0.005	140
Weight	0.375**	0.000	140
B. Urea	0.762**	0.000	140
S. Creatinine	0.323**	0.000	140
Tc	0.945**	0.000	140
Tg	0.956**	0.000	140
HDL	0.819**	0.000	140
LDL	0.858**	0.000	140
Vit. D	0.944**	0.000	140

5. DISCUSSION AND CONCLUSION

This study was limited by the small sample size and lack of further up-follow to the patients, as well as arandom selection of the study groups and the possible confounders that were not excluded when selecting the patients and control groups. In addition to little available previous studies of the same topic. Further studies are therefore suggested to have a larger study group, in addition to determining the possible cause of the remarked correlations. The values of interleukin 17 and 37 were considerably higher in the patients' group. Interleukin 17 and 37 were significantly correlated with fasting blood sugar and hemoglobin A1c. Interleukin 17 and 37 were negatively correlated to age and body mass index and Glycemic status was found to be negatively correlated with weight, age, blood urea vitamin D, and dyslipidemia. Diabetes mellites type two is a serious health condition that has many well-documented risk factors, recently the role of low-grade inflammation has been widely recognized and studied. Interleukin 17 is a proinflammatory cytokine that has been linked to the etiology of insulin resistance in type 2 diabetes Zareian *et al.* (2014), because of its abundance, interleukin 37 has been related to a protective impact against insulin resistance and enhanced insulin sensitivity (Li *et al.* 2019). These hypotheses were investigated in our study and the results were as shown above. Interleukin 17 levels in the patients' group were considerably greater than in the control group, which was consistent with prior study findings Büsing *et al.* (2013), Mominzadeh *et al.* (2014), Zareian *et al.* (2014) who also discovered such a significant correlation. In our study, it was also shown to be strongly linked with both fasting blood sugar and hemoglobin A1c levels, in agreement with the conclusions of Surendar *et al.* (2011), Kandeel *et al.* (2012) that revealed a substantial association between fasting blood glucose levels. While studying the relationship between interleukin 17 and other parameters, it was found that interleukin 17 was negatively correlated with both age and body mass index, the studies made by Surendar *et al.* (2011), Kandeel *et al.* (2012) both showed such a correlation with the age of the studied group, Kandeel *et al.* (2012) also illustrated the positive correlation with body mass index alongside with two other studies by Sumarac and Arababadi (Sumarac *et al.* 2009, Arababadi *et al.* 2010, Kandeel *et al.* 2012). Interleukin 37, on the other hand, was shown to be raised in older people as a defensive mechanism against insulin

resistance by decreasing gut microbiota dysbiosis, according to research (Li *et al.* 2019). These results are comparable to what was found by our study, as the levels of interleukin 37 were found to be significantly higher in the patients' group and were positively correlated with the level of blood glucose measured during fasting and hemoglobin A1c levels in the blood, but the protective role suggested by the above-mentioned study was not studied in this letter. On the other hand, a study by Wang *et al.* (2019) found that interleukin 37 be decreasingly expressed in patients with gestational diabetes, and another study found that it was negatively correlated with insulin level (Moschen *et al.* 2011). In our study, we found the level of interleukin 37 to be negatively associated with both weight and age, which was in accordance with what was found by the above-mentioned study by Moschen *et al.* (2011) who found a significant negative correlation with the body mass index. hemoglobin A1c and fasting blood glucose was found to be negatively correlated with age in this study, while it is a globally identified risk factor of the disease and documented by many studies (Ebenezer *et al.* 2003, Burattini *et al.* 2006), this difference in results can be due to other confounders and the small age range taken by our study making this negative correlation less reliable. Obesity is another well-known risk factor that has been linked to blood glucose and hemoglobin A1c levels in numerous research looking at the relationship between BMI and blood glucose levels (Meisinger *et al.* 2006, Kahn and flier 2000) while in our study negative correlation was found with weight, this difference in results may be because the factor studied in our letter is the weight rather than the body mass index. While studying vitamin D effect on glycemic status, we observed a significant negative association between the two as was suggested by two other studies done by (Zittermann *et al.* 2003, Borissova 2003). Blood urea level was also found to be significantly correlated to the level of glucose in blood and HbA1c in our study and other studies studying the correlation (Idonije *et al.* 2011, Shrestha *et al.* 2008, Bamanikar *et al.* 2016). We found that dyslipidemia (increased low-density lipoprotein, triglyceride, and cholesterol, and decreased level of high-density lipoprotein) as previously established by research, was highly connected with higher blood glucose levels and found by Suryawanshi *et al.* (2006), Nakhjavani *et al.* (2006), Otamere *et al.* (2011) among others.

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