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Research Article

Study of SIRPα gene expression in diabetic patients in Kirkuk city

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Abstract
The pathogenesis of type 1 and type 2 diabetes mellitus involve altering different immunological pathways which in turn affect host immune response and their genetic variations that will be affected as well. In order to overcome these physiological outcomes, many studies investigated the role of gene targeting to tackle diabetes. However, the role of immunoregulation and gene expression is still poorly studied. Therefore, this study aims to determine the role of signal regulatory protein alpha (SIRP-α) gene expression and related biochemical parameters in diabetes. 120 blood samples were collected (20 healthy and 100 diabetic patients), aged between (20-65) years, collected from Azadi Teaching Hospital in Kirkuk from February 2024 to April 2024. Samples were divided into three groups, the first group for patients with type 1 diabetes (Type 1) n= 50 samples, the second group for patients with type 2 diabetes (Type 2) n=50 samples, and the third group was 20 samples for healthy people. Results of the current study showed significant differences (P-Value < 0.01) between cumulative sugar, random blood sugar, fasting blood sugar, total cholesterol, high-efficiency lipids, very low-efficiency lipids, and low-efficiency lipids, compared to healthy groups. Significant differences were observed between the study groups in the SIRP-α protein levels, as an increase in the SIRP-α concentration was observed in type 1 diabetes (15.77±7.98) compared to type 2 (12.90±6.86) and the control group (8.53±5.18). Relative gene expression results show down regulation of SIRP-α gene expression in diabetic patients (T1D and T2D) compared with control group indicative of enhanced immune response in diabetes. This study concludes that both protein levels and gene expression of SIRP-α are altered in diabetes which might shed a light in contributing this marker in the immunotherapy control of diabetes.

Key words: SIRP-α, type 2 diabetes, type 1 diabetes, lipid profile, blood sugar, gene expression

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Introduction

Diabetes mellitus (D.M) is a chronic disease resulting from various factors, whether genetic, viral, environmental or functional. It is not a single disease, but rather several diseases that affect the body's organs in general and share a basic physiological condition, which is high levels of glucose (hyperglycemia) in the blood serum (1). Diabetes is a chronic disease and its causes are due to many environmental and genetic factors that lead to high blood glucose due to low levels of insulin secreted by the pancreas. (2)

Genetic factors are known to be strongly associated with diabetes, and the risk of developing the disease is associated with the genes of the Human Leukocyte Antigen (HLA) region located on chromosome 6 of the short arm 6p21 and are characterized as risk genes and susceptible to diabetes (3).

Diabetes is a major threat to human health, as it contributes to tissue dysfunction and many diseases associated with aging such as diabetes and cardiovascular diseases. This phenomenon can occur in response to a large number of stressors such as DNA damage, weak telomeres, ionizing radiation, and high concentrations of glucose. Scientists have found that genetic

changes do not occur arbitrarily, but there are reasons that stimulate their formation. These reasons may be internal or external factors (4).

Diabetes has several types, the most famous of which are type 1 diabetes and type 2 diabetes, which may exceed 90% of all diabetes cases worldwide. Although the pathogenesis and causes of type 2 diabetes are still not completely clear, it is certain that the disease develops as a result of an interaction between genetic predisposition and environmental factors such as nutrition and Western diet. Over the past decades, scientific knowledge about type 2 diabetes and its causes has accumulated significantly, as many genetic variations have been linked to the development of the disease and pancreatic beta dysfunction. Recently, genetic association studies at the genome level have been able to reveal and identify more than 140 common genetic variants associated with diabetes or glucose/insulin levels (5).

CD47 is an integral membrane protein consisting of an N-terminal extracellular IgV-derived immunoglobulin family motif followed by a five-part presenilin and ending with a short variably spliced cytoplasmic sequence (6). A long-range disulfide bond links Cys33 in the IgV domain to Cys263, the last extracellular loop in the transmembrane domain, and is essential for some of the signaling functions of CD47 (7).

CD47 is a highly glycated protein distributed on the surface membrane of several cells including red blood cells and non-hematopoietic cells, but its expression levels vary according to cell types. It is said to mediate immune homeostasis, cell proliferation, migration, phagocytosis, and cell death. CD47 performs these functions by binding to different ligands (SIRPa, thrombospondin 1) (TSP-1, thrombospondin-1, and integrin -8)SIRPa is also known as tyrosine phosphatase protein (SHPS-1) and is mainly expressed on the membranes of myeloid cells such as macrophages, dendritic cells, and monocytes (8)

TSP-1 is an extracellular glycoprotein composed of components of extracellular matrix and cell surface receptors that is secreted by macrophages, monocytes, platelets, and a variety of non-hematopoietic cells (9). It is a protein found on the surface of many cells throughout the body. It instructs circulating immune cells known as macrophages not to engulf these cells. CD47 acts as a "don't e at me" signal to macrophages in the immune system, making it a potential therapeutic target in some cancers. The body uses CD47 to protect cells that need to be protected and to help clear out old or unhealthy cells (10). Recent studies have shown that CD47-deficient somatic cells lead to dysfunction of important pathophysiological functions in cardiovascular homeostasis, immune regulation, cell and tissue resistance to stress, and chronic diseases of aging including cancer.

CD47 is known as Integrin-associated protein (IAP) and is encoded in humans by the CD47 gene, which belongs to the Immunoglobulin superfamily and shares with membrane integrins and also binds to Thrombospondin-1 (TSP1) and signal-regulating protein alpha (SIRP-a).

The interactions between SIRP-a and CD47 have been extensively studied in the immune system, where they play a very specific role. SIRPa inhibits phagocytosis rates and reduces the active engulfment of CD47-bearing cells, as this mechanism is subverted to be used by some cancer cells (including some endocrine and pancreatic tumors) that express CD47, thus reducing their ability to be targeted and eliminated by cells of the innate immune system. In addition, the mechanism may be relevant to diabetes (11). Clinical studies have shown that abnormal expression of TSP1 is positively associated with obesity, liver disease, and diabetes (12). CD47, SIRPa may form part of a series of mechanisms deployed by pancreatic B cells to resist cytotoxic activity in diabetes (13). CD47, SIRPa play important roles in immune regulation and have a tendency to interact within the boundaries of the islets of Langerhans to regulate cell viability. As such, the physiological role of these proteins likely extends beyond their previously ascribed ability to influence the phagocytic activity of macrophages, and in the context of islet autoimmunity, their interactions may directly influence B-cell viability (SIRP-a is present on pancreatic B cells and is regulated by anti-inflammatory cytokines**.** There are still few studies on this topic presented (14,15). The current study therefore, aims to investigate the SIRP-α gene and protein levels in diabetic patients.

Materials and Methods

Sample collection:

Blood samples were collected from 120 diabetic patients and controls (20 healthy and 100 patients) were collected, 60 of them were females and 60 males, aged between (20-65) years, they were collected from Azadi Teaching Hospital in Kirkuk from February 2024 to April 2024. The samples were divided into three groups, the first group for patients with type 1 diabetes (Type 1) n=50, the second group for patients with type 2 diabetes (Type 2) n=50, while the third group was 20 samples for healthy people. diabetes was diagnosed in patients by doctors specializing in diabetes in the hospital's diabetes unit. A special form was organized in which information was collected for patients with type 1 and 2 diabetes and healthy people, information about age, gender, weight, and height, the healthy group was for people with no family history of diabetes.

SIRP-α protein level detection by ELISA:

This ELISA kit uses the Sandwich-ELISA principle. Chinese-origin kits (Biotech), following the manufacturer's instructions. The ELISA microplate provided in this kit is pre-coated with an antibody specific for SIRP-α. Samples (or standards) are added to the wells of the ELISA microplate and combined with the specific antibodies. Then the biotinylated detection antibodies for (SIRP-α) and Avidin-Horseradish Peroxidase (HRP) conjugate are added together to each well of the plate and then incubated. The free components are washed away. Substrate solution is added to each well. Only those wells containing the antibody to detect human biotinylated SRIP-α and the Avidin-HRP conjugate will appear blue. The enzyme-substrate reaction is terminated by adding stop solution and the color turns yellow. Optical density (OD) is measured spectrophotometrically at a wavelength of 450 nm. The OD value is proportional to the concentration of human SIRP-α. The concentration of human SRIP-α in the samples can be calculated by comparing the OD of the samples with the standard curve.

Serum was obtained from blood samples after collection of the whole blood, allow the blood to clot by leaving it undisturbed at room temperature. This usually takes 15–30 minutes. Remove the clot by centrifuging at 1,000–2,000 x g for 10 minutes in a refrigerated centrifuge. The resulting supernatant is designated serum .Sandwich-ELISA was performed following

manufacturer's instructions (Macrogene, Korean the procedure is detailed in Ismael, A., & Jabbar, S. in 2024 (14) standard curve was made using stock solution and following diluted concentrations. SIRP-α protein concentration was calculated depending of the linear regression fit equation on the standard curve plot.

Molecular determination of expression About SIRP-α genes

The FavorPrepM Blood/Cultured Cell Total RNA Mini Kit was used to isolate total RNA from human whole blood based on the mini spin column (silica matrix) technique (Favogene Ltd, Korea.(Human Differentiation Kit for SIRP-α Primers).The specific primer for SIRP-α gene expression (Macrogen DNA Technologies, Korea) was determined by the researcher based on the NCBI standard gene bank and using the web-based primer design tools. The specific primers for all CD markers are listed in Tables (1). The primers come in lyophilized powder and a stock solution is made by dissolving them in 250 µl of nuclease-free water to a stock solution of 100 µmol/L, and a working solution of all primers is prepared by diluting the stock to 20 µmol/L using the equation (C1*V1=C2*V2).

Table (1): Primers for the SIRP-α gene

Primer	Sequence	Tm (°C)	GC (%)
Forward	5'- GCTCCAAGAATATCCTAGCC - 3'	60	50
Reverse	3'- GGCTCCTCTCCACCACATCC - 5'	66	65

Statistical Analysis

SPSS-22 was used to evaluate all study tests. P values less than 0.05 indicate significant differences; P values greater than 0.05 indicate no differences.

Results

Distribution of patients according to study groups

This research chose a random sample of diabetics from Kirkuk Governorate, Iraq. In general, the study samples were separated into three groups: healthy (20: 10 males and 10 females), type 1 diabetes (25: 12 males and 13 females), and diabetes without obesity. Blood samples were taken in February and April 2024.

Distribution of lipid and glucose levels among study groups

The results in Table (4.1) showed a significant difference in P-Value between hemoglobin A1c (HbA1C) and random blood glucose ((PPG and Fasting blood glucose FBG)) and cholesterol (Chol). High Density Lipoprotein (HDL), very low density lipoprotein ((VLDL) and Low Density Lipoprotein ((LDL) respectively (0.00009, 0.00002, 0.0008, 0.025, 0.025, 0.046, 0.024) compared to healthy groups. P-value (0.00009). In addition, the distribution of lipids and glucose level between the control group and cases is shown in the figure (1) and (2) respectively.

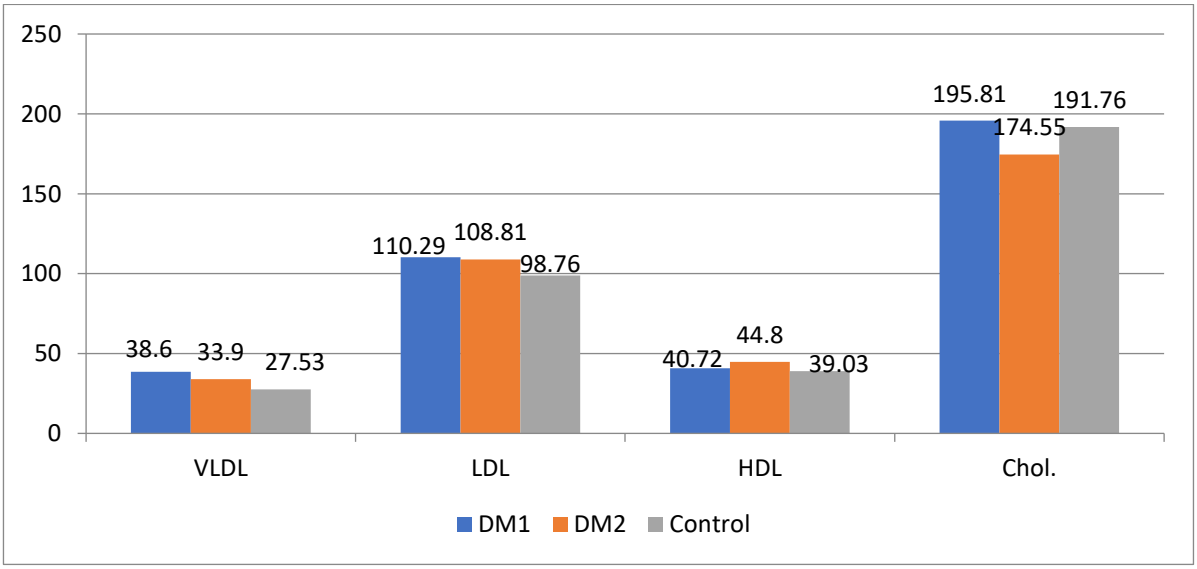

Figure (1): Distribution chart of fat profile among study groups

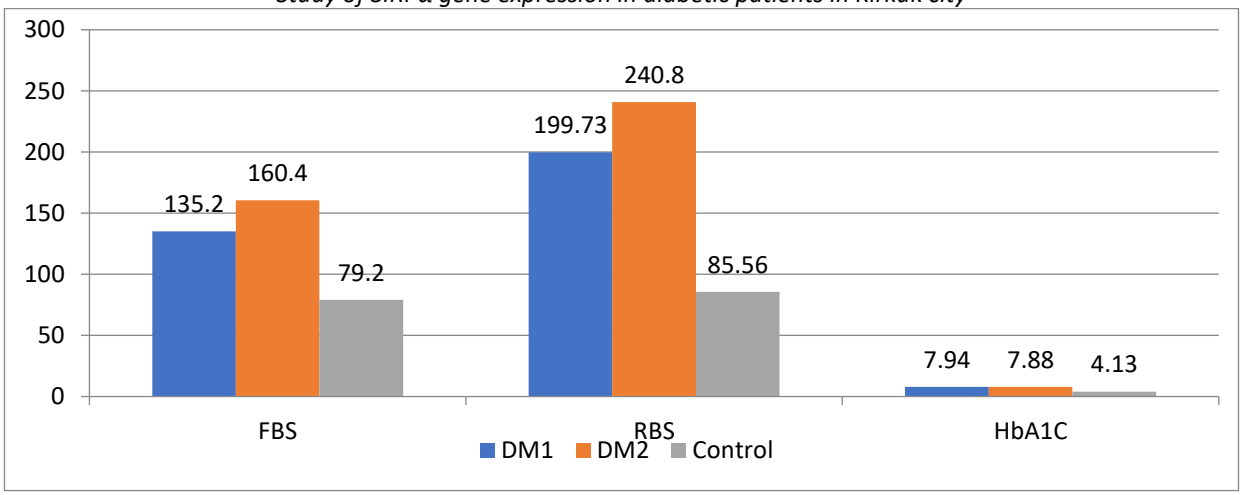

Figure (2): Scatter plot of glucose level distribution among study groups

Distribution of lipid levels by gender among study groups

Compare the mean ± SD and p-value of VLDL between males and females in Table (2). More statistical tests found no significant differences between men and women in the study population. Our results indicates lower mean ± SD values in the control group compared to both diabetes groups. Females had somewhat higher mean ± SD values than men in both the control and type 2 diabetes groups, but the type 1 diabetes group had a near mean value.

Table (2): Lipid levels for diabetics and healthy people by gender

Control			DM2			DM1			
p-value	**F**	**M**	**p-value**	**F**	**M**	**p-value**	**F**	**M**	
0.02	32±11	28±12	0.127	34±14	35±16	0.85	33±15	.315 ± 34	**VLDL**
0.10	127±28.9	116.4±41	0.0248	86.1±44.7	113.4±52.3	0.25	114.4±38	116.2±31	**LDL**
0.13	40.2±5.4	36.4±4.7	0.69	45.9±25.1	33.8±6.7	0.46	37.6±6.6	35.7±93	**HDL**
0.43	173±67	140±61.6	0.86	155±68.2	156±73	0.82	180±8.1	189±88.3	**TG**
0.7	171±87	179±6	0.6	170±34	184±23	0.81	178±65	180±7	**Chol**

Table 2-4 displays mean ± SD triglycerides (TG) levels for males and females**.** The current investigation found no significant gender differences. The study found higher mean ± SD values in type 1 diabetes patients compared to other groups, with males having the greatest value compared to females. The value was equivalent for men and women with type 2 diabetes. While the Table (2) shows the mean ± SD and p-value of HDL levels in males and females. The study demonstrated a statistical difference (p-value = 0.0246) between men and women with type 2 diabetes. Note that girls had a greater mean ± SD value than males in all research groups. A significant difference (P = 0.02) was found in the mean ± SD and p-value of low-density lipoprotein (LDL) between males and females in the control group. According to Table (4-2), males had a greater mean value ± SD than females in all research groups.

Distribution of glucose levels by gender among study groups

The attributes of the research participants, categorized according to their blood glucose level, are presented in Table (3). Descriptive statistics, including the mean and standard deviation, were calculated to compare males and females. The findings of the fasting blood glucose (FBG) test indicated that there were no significant differences between men and females in all study groups. However, there was a modest rise in the average ± standard deviation (SD) of FBG levels in females compared to males in both groups of diabetes patients. In the postprandial glucose test, a statistically significant difference was seen between males and females in the group of patients with type 2 diabetes (P value = 0.033). However, in the other groups, there was a little rise in the average ± standard deviation for females compared to males, but it did not achieve statistical significance. The hemoglobin A1c (HbA1c) test revealed a notable disparity between males and females in the healthy group (P value = 0.024). In the other groups, there was a marginal elevation in the mean ± SD for males in comparison to females. However, it is worth noting that diabetes is prevalent in the study area and is associated with other diseases, either directly or indirectly. The research groups were analyzed to compare the lipid profile between males and females. Based on the findings of FBG and HbA1c, it is seen that there is a higher glucose level in males compared to females in both patient groups. However, this difference is not statistically significant.

Table (3): Glucose level for diabetics and healthy people by gender

Control			DM2			DM1			
p-value	**F**	**M**	**p-value**	**F**	**M**	**p-value**	**F**	**M**	
0.382	5.23±0.3	5 ±0.3	*0.033*	7.6 ±1.8	8±1.7	0.817	6.86 ±1.2	7±0.7	**HbA1c%**
0. 41	83.9 ±7.4	83.32 ±8.6	0.41	*166.5 ±70.4*	182.5 ±63.9	0.878	127 ±44.5	133.68 ±37.5	**FBS(mg/dl)**
0.024	92.9 ±7.4	93.32 ±8.6	0.177	*204.15 ±69.4*	243.5 ±63.9	0.356	194.35 ±51.6	175.2 ±35.6	**RBS(mg/dl)**

Immunological study of the SIRP-α variable

The results of the current study found significant differences between the study groups in the SIRP-α rate, as an increase in the SIRP-α rate was observed in type 1 diabetes (15.77±7.98) compared to type 2 (12.90±6.86) and the control group (8.53±5.18) as shown in Table (4), Figure (3).

Table (4): SIRP-α concentration levels in the studied groups

p-value	Control	DM2	DM1	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
0.0026	8.53±5.18	12.90±6.86	15.77±7.98	**SIRP-α**

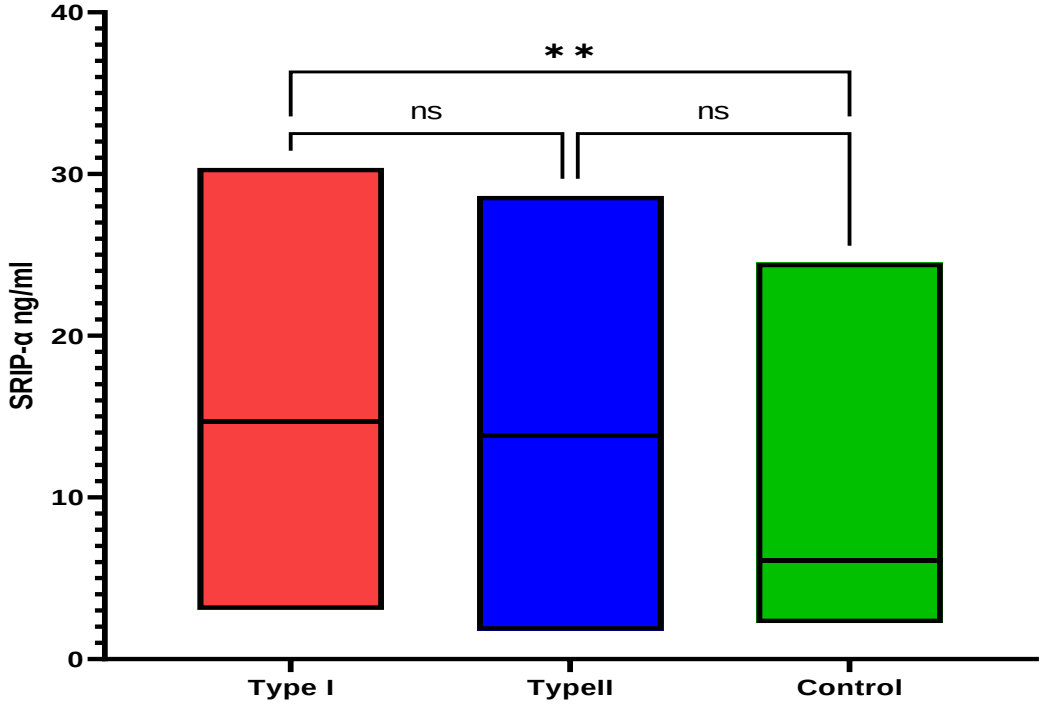

Figure (3): SIRP-α concentrations among the research

SIRP-α gene expression in the studied groups

The genetic investigation revealed that the control group had considerably elevated levels of SIRP-α gene expression, with an average fold change of 1.00, compared to the type 1 diabetes group, which had an average fold change of 0.08. The genetic investigation revealed that healthy patients had much greater levels of CD47 gene expression, with an average fold change of 1.00, compared to those with type 2 diabetes, who had an average fold change of 0.04. These findings are illustrated in Figures 4 and 5.

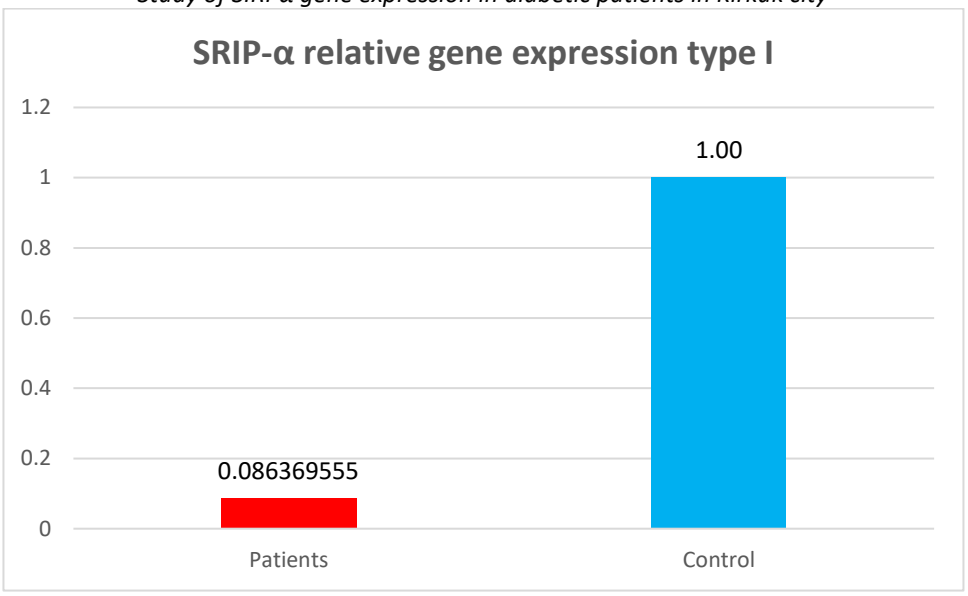

Figure (4): Gene expression of SIRP-α in the patient group (type I) and the control group.

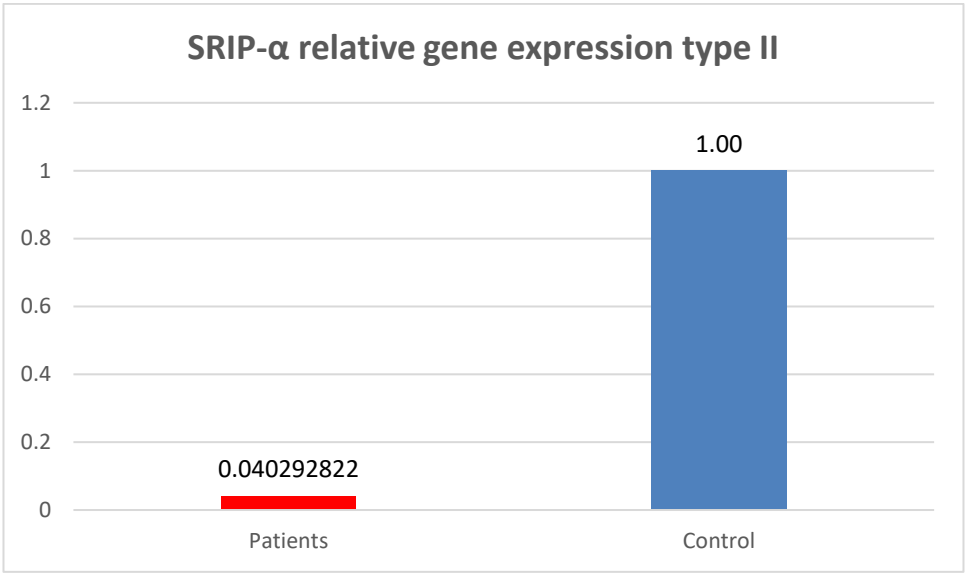

Figure (5): Gene expression of SIRP-α in the patient group (type II) and the control group.

Discussion

The current study revealed significant statistical disparities in lipid profile levels between individuals with diabetes and the healthy group. It is worth noting that there are variations in lipid levels between the two patient groups and the healthy group. The variation in nutrition, age, gender, and genetic makeup among individuals may account for the observed variances (16,17). Conversely, prior research have demonstrated a negative correlation between BMI and the profile. Statistically significant variations in blood glucose levels can be found across the research groups. It is important to mention that individuals with type 2 diabetes have greater glucose levels than those with type 1 diabetes. The explanation is that persons with type 2 diabetes have a more severe form of the disease. The study's findings demonstrated the impact of diabetes on the level of total cholesterol (TC). Specifically, the TC value was seen to be greater in individuals with type 1 diabetes compared to those with type 2 diabetes and healthy individuals, as depicted in Figure (4-1). The group with type 1 diabetes had the highest value, and there was a direct association between the glycemic index and total cholesterol, meaning that as the glycemic index increased, so did the total cholesterol number. The rise in cholesterol levels can be attributed to dietary patterns, which is one of the contributing factors to elevated fat concentration in the bloodstream. This, in turn, leads to an increase in cholesterol levels. Additionally, the body's efficient production and elimination of cholesterol also play a role in this phenomenon. This study confirmed the findings that fat cells in the abdominal area have a significant impact on lipid imbalances in individuals with diabetes, compared to fat cells in other parts of the body. Additionally, central fat cells contribute more to insulin resistance and are more efficient in recycling fatty acids during lipolysis. Multiple studies have also shown that the levels of high cholesterol are influenced by both the composition of diet and hereditary factors, such as inherited cholesterol and obesity (18). Taskinen et al. (19) determined that an increase in fat mass

around the waist circumference significantly contributes to the elevation of total cholesterol levels due to metabolic imbalance (20). Upon examination of Table (1), it was determined that there were no notable disparities in the HDL levels between individuals with type 1 diabetes (40.72 b) and those who were in good health. The study conducted by Cai et al. (21) revealed a decrease in HDL-C levels, whereas there was an increase in triglycerides, cholesterol, LDL-C, and VLDL-C levels. Diabetes impacts the levels of High-density lipoprotein (HDL-C) due to the elevated concentrations of both chylomicrons and VLDL-C. For instance, consuming a meal that is high in sugar leads to an increase in the synthesis of hepatic triglycerides and the secretion of VLDL-C. Liver cells store triacylglycerol as lipid droplets, which can be used to produce VLDL-C. Mustafa's 2018 study confirmed that low HDL-C levels had a detrimental impact on lipid values and highlighted the crucial role of HDL-C in removing excess cholesterol from cells and transferring it to the liver through the bloodstream. Consequently, reduced levels of high-density lipoprotein (HDL-C) result in a decline in the efficiency of cholesterol utilization (22). The study also validated that a reduction in the level of HDL-C is associated with health issues in individuals, including heart disease and atherosclerosis, caused by the buildup of lipids on the inner walls of the circulation. Additionally, it results in the impairment of its functional characteristics (23). The present study examined the impact of diabetes on VLDL-C and LDL-C levels. The findings revealed significant differences, with an increase in VLDL-C and LDL-C values observed in the diabetic sample, while a decrease was observed in the control group. Additionally, a positive correlation was observed between VLDL-C and LDL-C levels, indicating that an increase in both diabetes indicators corresponded to an increase in their values. The elevated levels of LDL-C and VLDL-C can be ascribed to two factors: Initially, the absence of insulin triggers the breakdown of stored fats in adipose tissues, causing an elevation in the levels of specific compounds (LDL-C, VLDL-C). This increase is a consequence of the activation of the lipoprotein lipase enzyme in adipose tissue, which prompts the release of fats into the bloodstream. Furthermore, the rise in oxidative stress is linked to the pathological symptoms of metabolic syndrome, and the reduced density of low-density lipoprotein (LDL-C) is connected to its heightened susceptibility to oxidative stress. Since LDL-C is a primary component of metabolic syndrome, this leads to an imbalance in body fat levels, which is evident in cases of diabetes. Jung et al. (24) observed that insulin resistance arises from a dysfunction in adipose tissue function, leading to elevated levels of VLDL-C and TG.

The triglyceride test findings revealed a significant average rise in the diabetes groups as compared to the healthy group, with a noticeable emphasis on the majority of the increase being observed in men. Except for the average TG level in healthy women, which was greater than in males, comparing the results with those of previous research reveals that an elevated TG level is linked to the risk of diabetes in both genders (25). Within the healthy group, there is a larger proportion of females compared to males. These findings contradict prior studies suggesting that adult males often had higher triglyceride levels than women (26). The utilization of triglyceride-glucose is highly likely to be beneficial in the prediction of Type 2 Diabetes Mellitus in a clinical setting. It perhaps acts as a mediator in the relationship between BMI and the likelihood of developing T2DM (27). This might be attributed to variations in female age, lifestyle, ethnicity, and genetic factors. Based on the total cholesterol results, there were no statistically significant variations between the study groups. However, the concentration level was nearly the same in type 1 diabetes. In both the healthy group and type 2 diabetes, females had a lower average concentration compared to males. Significant variations in total cholesterol levels typically result in an increased susceptibility to diabetes (28). Diabetic individuals often have reduced total cholesterol levels (29). Consistent with the present findings, prior research has demonstrated that diabetic males exhibit elevated levels of total cholesterol compared to diabetic females (30). Furthermore, there are additional variables that contribute to the disparity in gender, such as the observation that before to menopause, women had greater levels of total cholesterol compared to males of same age. The findings of HDL_C testing revealed no statistically significant disparities between males and females in both the diabetes and control groups. However, the average HDL_C level was consistently higher in females compared to males throughout all research groups. Generally, having low levels of HDL_C is linked to an increased risk of developing diabetes. Based on recent research, past studies have demonstrated that women have elevated levels of HDL_C compared to males (31). Prior to menopause, women have greater levels of HDL_C compared to males of the same age due to the influence of the female sex hormone estrogen, which seems to enhance the production of this beneficial cholesterol. Aside from gender, disparities in HDL levels may arise due to factors such as race, ethnic groupings, and regional variations. As an illustration, individuals of American Indian descent possess the R230C (rs9282541) mutation in the ABCA-1 gene, which is linked to reduced levels of high-density lipoprotein cholesterol (HDL-C), obesity, and type 2 diabetes (32).

There are statistically significant variations between males and females in the type 2 diabetes group when it comes to LDL_C. There is no statistically significant disparity between males and females in both the healthy group and the group with type 1 diabetes. Overall, persons with diabetes do not have greater LDL_C values compared to individuals without diabetes, even taking into account factors such as age, sex, and body weight (33). Following menopause, levels of LDL_C tend to increase, often surpassing those of males in the same age group. Conversely, obesity elevates the production of low-density lipoprotein cholesterol by the liver (34). Furthermore, there may be a notable impact of genetic factors, since high LDL_C levels might be inherited in certain instances. Familial hypercholesterolemia is a hereditary disorder that is characterized by abnormally elevated levels of LDL_C (low-density lipoprotein cholesterol). There is no statistically significant disparity between males and females in all research groups with regards to VLDL-C findings. Both type 1 diabetes and type 2 diabetes are linked to higher levels of VLDL_C concentration (36). These findings align with previous studies that have demonstrated substantially elevated levels of VLDL_C in individuals with obese type 2 diabetes (37). Multiple prior research have shown that fasting plasma glucose (FPG) and glycated hemoglobin (HbA(1c)) levels are elevated in males compared to females (38). The PPG test findings

showed that there were no significant variations in glucose levels between girls and males in both the control and diabetes groups.

The disparity in glucose absorption between males and females is the underlying cause of this variation (39). It is important to mention that there was a rise in the RBS level among males, which showed a significant difference in patients with type 1 diabetes (P = 0.033). Additionally, the findings indicated an increase in the HbA1c concentration among females, which also showed a significant difference in the control group (P = 0.024). The presence of sex differences between males and females can be attributed to several factors, such as variations in sex chromosomes, gene expression, sex hormones, anatomy, and physiology (40). Furthermore, there are several aspects such as age, lifestyle, food, environmental factors, and certain linked disorders.

The work conducted by (41) indicates that disruptions or abnormalities in SIRPα might enhance the engulfment, processing, and abnormal presentation of self-antigens to T cells, contributing to the development of T1D.

Recent studies have demonstrated the participation of the SIRPα signaling pathway in maintaining a stable immune system and in controlling the functioning of brain networks. Recent progress in studying the structure and function of the SIRPα signaling pathway offers promising indications for the potential therapeutic advantages of modulating this signaling system in autoimmune diseases, diabetes, and neurological illnesses (42). A prior investigation documented the activation of signal regulatory protein (SIRPα) and observed that a lack of SIRPα was linked to reduced viability of beta cells. The presence of these anti-apoptotic proteins and their associated cytoprotective effects were eliminated following the STAT6-mediated reduction in pancreatic beta cells (43,44).

Kulkarni *et al.,* (45) discovered that SIRPα hinders the process of phagocytosis of normal host cells. SIRPα forms a connection with the integrin CD47, which is found in many different tissues. Apoptosis causes CD47 to shift from being concentrated in certain areas on the cell surface to being spread out, resulting in a decrease in its ability to bind to SIRPα. This decrease in binding lessens the negative signals that limit the removal of dead cells by phagocytosis in diabetic patients.

SIRP is composed of a group of genes, including SIRPα, SIRPβ, and SIRPγ proteins, that are believed to have emerged by gene duplication. The extracellular domains of these entities exhibit a significant degree of similarity and possess the distinctive features of the immunoglobulin superfamily. In contrast, their intracellular domains, which govern their signaling mechanisms, display a considerable degree of diversity (46). The SIRP family is classified as "coupled receptors," which consist of both activating and inhibitory receptors. Notably, the cellular expression and function of CD47 ligands also differ. The functional role of the polymorphic SIRPα protein has been thoroughly investigated in myeloid cells, where it is actively expressed (47). In addition, a recent study examining the entire genome has revealed a strong connection between the 20p13 region, which includes the SIRP cluster, and the vulnerability to type 1 diabetes in humans. Significantly, the SIRP cluster comprises three genes, namely SIRPD, SIRPB1, and SIRPG, which are known to encode functional ligands to CD47 in diabetes patients. This knowledge is based on linkage disequilibrium (LD) analysis (48). SIRP-α is responsible for encoding a group of interconnected receptors that transmit both stimulating and inhibitory signals and are linked to the risk of type 1 diabetes (T1D). Wong et al. (49) conducted a study where they discovered that SIRP-α, which encodes an inhibitory receptor on myeloid cells, is a gene located at the insulin-dependent diabetes locus 13.2 (Idd13.2). This gene is responsible for causing islet inflammation and type 1 diabetes (T1D). In comparison to strains that are resistant to T1D. using nanoparticles is suggested for future research in targeting SIRP-α gene in cancer patients who suffer from diabetes, because nanoparticles recently showed promising result in cancer research (50).

To conclude, in this study, diabetes mellitus led to disturbance of vital indicators such as total lipids, triglycerides, random and fasting blood sugar, low-efficiency lipids and very low-efficiency lipids, which were negatively reflected by their significant changes leading to other health problems. The results of the current study showed a relationship between the diabetes group and the level of SIRP-α, as an increase in SIRP-α levels was observed in type 1 diabetes compared to type 2 and the control group. The results of the genetic study showed that the levels of relative gene expression of SIRP-α were significantly higher in the control group compared to the type 1 and type 2 diabetes group which indicate a negative regulation of SIRP-α gene and protein in diabetes.

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