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RESEARCH ARTICLE

Levels of IL-6 and TNF-α among Type 2 Diabetic Patients with Dyslipidemia and Insulin Resistance

Najlaa Jabaar Wasmi[1*], Ali Shalash Sultan[1]

Department of Biology, College of Science, Mustansiriyah University, Iraq.

***Corresponding Author Email:** *najlaawasmi@yahoo.com*

Abstract

This study was aimed to investigate the effect of type2 diabetes mellitus in Iraqi male patients on the levels of IL-6 and TNF-α and their relationship with IR and dyslipidemia. The study included (80) individual (males), (60) were diagnosed with type2 diabetic patients and (20) as healthy control group.IL-6 and TNF-α biomarkers were assessed in both control and diabetic groups. Results showed increasing levels of IL-6 in diabetic group ((9.065 ± 0.504) in comparison with healthy control group (4.186 ± 0.509), TNF-α was increased significantly ($p<0.05$) in diabetic group (44.222 ± 7.336) in comparison with control group (11.082 ± 1.204). FBG level was increased significantly ($p < 0.01$) in diabetic groups (233.90±11.12) in comparison with control group (92.90±240).HbA1cin diabetic group (7.59 ± 0.21) showed significant increase ($p < 0.01$) in comparison with control group (4.59 ± 0.11).Insulin showed high significant ($p < 0.01$) increase in diabetic group (18.24 ± 2.27) when compared with control group (6.74 ± 0.86).IR value was increased significantly ($p < 0.01$) in diabetic group (11.58 ± 1.89) when compared with control group (1.56 ± 0.21).Total cholesterol showed non- significant ($p> 0.05$) difference in diabetic group (188.83 ± 5.46) in comparison with control group (186.40 ± 7.47). Triglycerides value was increased significantly ($p < 0.01$) in diabetic group (208.05 ± 11.41) when compared with control group (125.55 ± 11.18).LDL showed non-significant ($p> 0.05$) difference in diabetic group (102.23 ± 4.29) in comparison with control group (111.85 ± 7.24).VLDL was increased significantly ($p < 0.01$) in diabetic group (41.95 ± 2.33) when compared with control group (23.99 ± 2.47).HDL showed non-significant difference ($p> 0.05$) in diabetic group (47.15 ± 1.15) in comparison with control group (50.46 ± 1.86).

Key words: *IL-6, TNF-α, Diabetes type2, insulin resistance (IR), Dyslipidemia.*

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both [1]. there are some differences in insulin secretion profiles between people who had normal weight and those obese people with T2DM, may be related with the degree of peripheral insulin resistance [2].

When the glucose concentration is high, insulin secretion is stimulated and carbohydrate is used instead of fat, and the excess blood glucose is stored in the form of liver glycogen, liver fat, and muscle glycogen and will be used by the cells for energy [3]. T2DM is a chronic inflammatory disease in which increased levels of cytokines are produced under various stimulithat Chronic low-grade inflammation is involved in the development of insulin resistance, which increases the risk of type 2 diabetes. Adipocytes secrete inflammatory cytokine; in addition they develop macrophage infiltration (adiposities) which is the source of almost all TNF–α and most of the IL-6 in adipose tissue along with other inflammatory markers [4].

Adipokines such as resistin and retinol-binding protein 4 decrease insulin sensitivity, whereas leptin and adiponectin have the opposite effect. Such cytokines are involved in obesity like IL-6and TNF-α which originate from macrophages in adipose tissue,[5].The typical dyslipidemia of obesity Characterized by increased triglycerides (TG) and FFA, decreased HDL-C with HDL dysfunction and normal or slightly increased LDL-C with elevated small dense LDL[6,7].

Materials and Methods

The subjects study included two groups of gender males: First healthy group (20) as control aged (40-55) years with mean ± SD of age (43.30 ±3.12) were included in this study. The second group (60) patients as diabetic group aged (40-55) years with mean ± SD of age (48.46 ±5.03), who visited the Specialist Center for Endocrine and Diabetes at Baghdad province.

Blood sample was collected from each individual after (12- 14) hours fasting (8 millilitres of blood), the blood sample was divided into two aliquots; 2 and 6 ml. The first aliquot blood was dispensed in a tube containing ethylene diamine tetra acetic acid (EDTA K3) as anticoagulant and stored at (2-8°C) for analyses of HbA1c, while the second aliquot was transferred into Gel tubes without anti-coagulant; blood was left to clot for 20-30 minutes at (37°C) in an incubator. Serum were separated by centrifugation at 3000 rpm for 10 minutes used for the determination of FBG, Insulin, lipids profile, IL-6, and TNF-α analysis (500 µl serum in Eppendorf tube).

- Fasting blood glucose was estimated by the mind ray Bs-200 [8].
- Hemoglobin A1C has been defined operationally as the "fast fraction" hemoglobin's (HbA1a, A1b, A1C) that elute first during column chromatography with cation-exchange resins. The non-glycosylated hemoglobin, which consists of the bulk of the hemoglobin has been designated HbA0. The present procedure utilizes an antigen and antibody reaction to directly determine the concentration of the HbA1c [9].
- Lipid profile (TC, TG, LDL, VLDL and HDL) determined by using the mind ray Bs-200 [8].
- Insulin was estimated by Cobase e 411 [10].
- The homeostatic model assessment of insulin resistance
- (HOMA-IR) is a widely used and calculated by fasting glucose (mg/dL) * fasting insulin (UI/L) / 405 [11].
- IL-6 and TNF-α, estimated by ELISA reader and ELISA printer [12].

Statistical Analysis

The Statistical Analysis System [13] program was used for effect difference factors in study parameters. ANOVA and T-test was used to significant compare between means. Estimation of correlation coefficient in this study between different parameters was done.

$$r = \frac{n(\Sigma xy) - (\Sigma x)(\Sigma y)}{\sqrt{[\,n\Sigma x^2 - (\Sigma x)^2\,]\,[\,n\Sigma y^2 - (\Sigma y)^2\,]}}$$

Results and Discussion

Table 1: shows FBG, HbA1c, Insulin, and IR (Mean ± SE) in control and diabetic groups

Groups	Mean ± SE			
	FBG (mg/dl)	HbA1c (%)	Insulin(µ/ml)	IR
Control	92.90 ± 2.40	4.59 ± 0.11	6.74 ± 0.86	1.56 ± 0.21
Diabetic	233.90 ± 11.12	7.59 ± 0.21	18.24 ±2.27	11.58 ± 1.89
T-test	7.273 **	8.218 **	2.881 **	3.044 **

FBG level was increased significantly ($p < 0.01$) in diabetic groups (233.90±11.12) in comparison with control group (92.90±240). Figure (1).

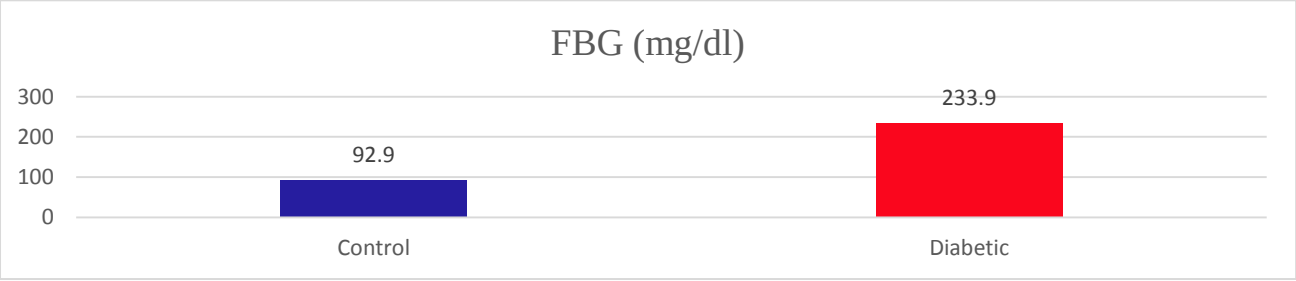

Figure 1: represents the FBG in control and diabetic groups

HbA1c in diabetic group (7.59 ± 0.21) showed significant increase ($p < 0.01$) in comparison with control group (4.59 ± 0.11). Insulin showed high significant ($p < 0.01$) increase in diabetic group (18.24 ± 2.27) when compared with control group (6.74 ± 0.86).IR value was increased significantly ($p < 0.01$) in diabetic group (11.58 ± 1.89) when compared with control group (1.56 ± 0.21). Figure (2).

Figure 2: represents the IR in control and diabetic groups

The increasing in the level of fasting blood glucose (FBG)(Table 1) was in agreement with many researchers [1,14]. That chronic diabetes is a group of metabolic diseases characterized by hyperglycemia, the elevation in FBG level may be resulting from both defects in insulin secretion and insulin action [15].The FBG test is directly proportional to the severity of the diabetes mellitus [16,17].

So the increase in the level of FBG in our results was also in agreement with that reported by [18] stated that FBG level ≥ 126 mg/dl when level of FBG in diabetic group compared with the control group. The level of glycated hemoglobin (HbA1c %) in diabetic group (7.59 ± 0.21) was increased significantly ($P<0.01$) in comparison with control group (4.59 ± 0.11).

The rises in the level of HbA1c % was associated with the increasing level of FBG in diabetic group So increased of HbA1c level in our study indicates poor control of blood glucose level or poor glycemic index [19,20]. Reported an increasing HbA1c level (9.7%) in T2 diabetics patients in Saudi population and [21] found HbA1c level (9.5% vs 6.0% in control). The International Diabetes Federation (IDF) recommend HbA1c values below 6.5% while American Diabetes Association (ADA) recommend that the HbA1c be below 7.0% for most patients to indicate good glycemic control [22].

The significant ($p<0.01$) positive correlation found in control based study between FBG and HbA1c was ($r = 0.780$),(Table2).This indicates that the higher level of FBG the higher glycosylation hemoglobin [23], and with that reported by [21] who found positive relationship between FBG and HbA1c ($r = 0.55$), and with that reported by [24] ($r=0.58$) in Iraqi T2DM patients. The two main causes of hyperglycemia in type 2 diabetes mellitus are impaired insulin secretion and increased insulin resistance. Evaluation of IR and function of ß-cell is important upon understanding the disease status and selection of pharmacologic treatment [25, 26].

Insulin level was increased in diabetic patients (Table 1), thus insulin is the principal hormone of glucose homeostasis; it stimulates glucose influx into muscle, glycogen synthesis in the liver and muscle, and fat deposition in adipocytes [27].Type 2 diabetes is evidenced by increased glucose levels in the blood, which results from elevated glucose production in the liver (gluconeogenesis and glycogenolysis) and decreased glucose uptake by muscle [26, 27].

Table 2: Shows the correlation coefficient of HbA1c with FBG, Insulin, IR, TG, VLDL, and BMI

Parameters	Correlation Coefficient of HbA1c	Level sig.
FBG	0.780	**
Insulin	0.228	*
I.R	0.333	**
TG	0.670	**
VLDL	0.406	**
BMI	0.281	**

*P<0.05, **P<0.01

HbA1cshowed positive significant ($p< 0.01$) correlation (0.780) with FBG. Figure (3). HbA1cshowed positive (0.228) significant correlation ($P<0.05$) with insulin. Figure (4).

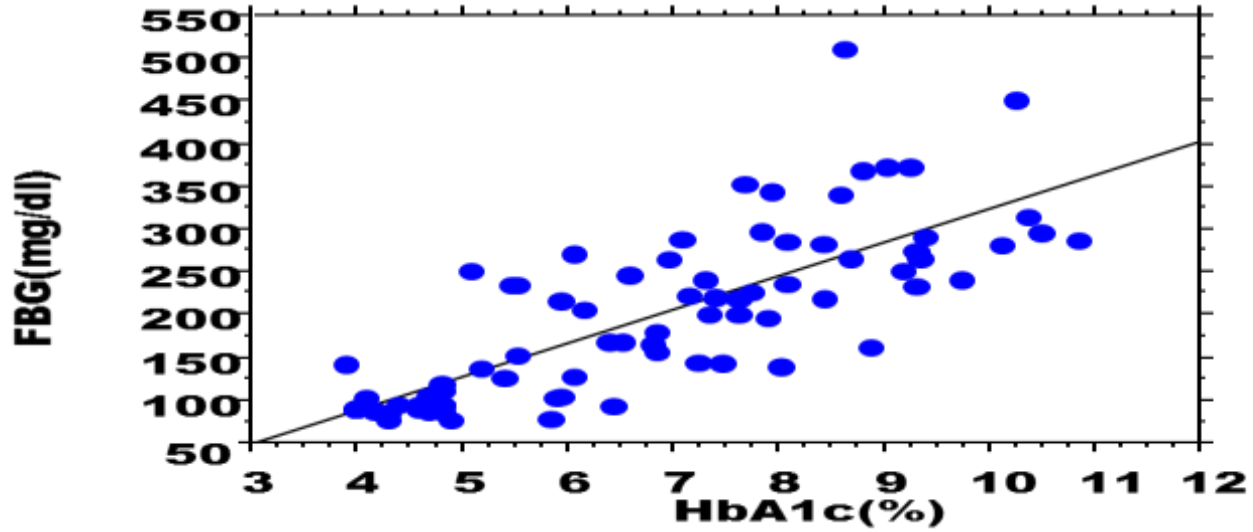

Figure 3: Represents correlation between HbA1c and FBG

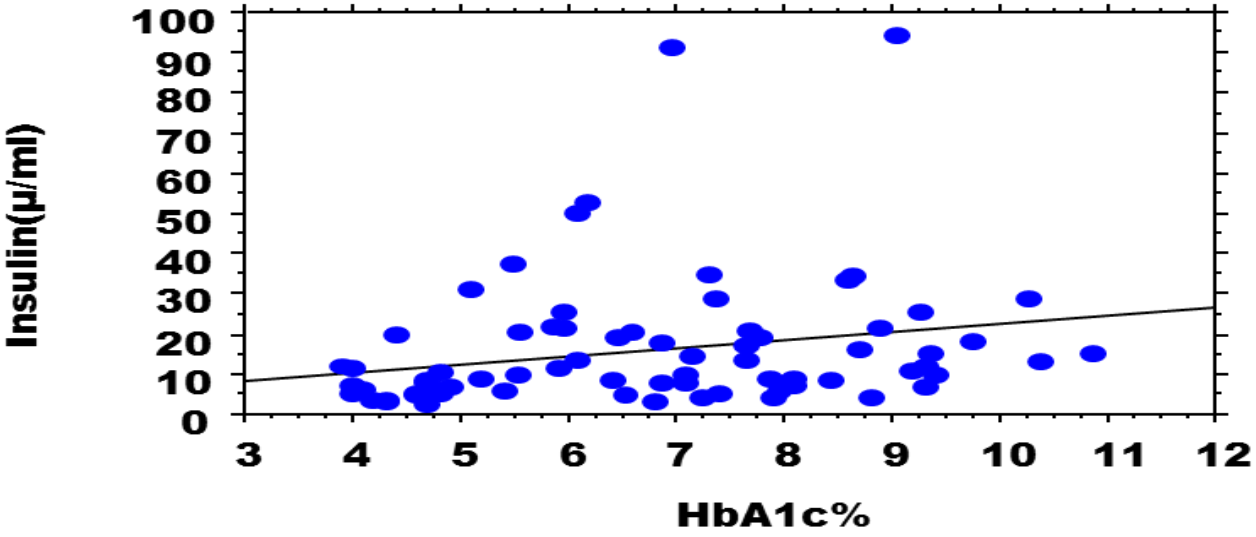

Figure 4: represents correlation between HbA1c and Insulin

HbA1c showed positive significant ($p < 0.01$) correlation (0.333) with IR. Figure (5).

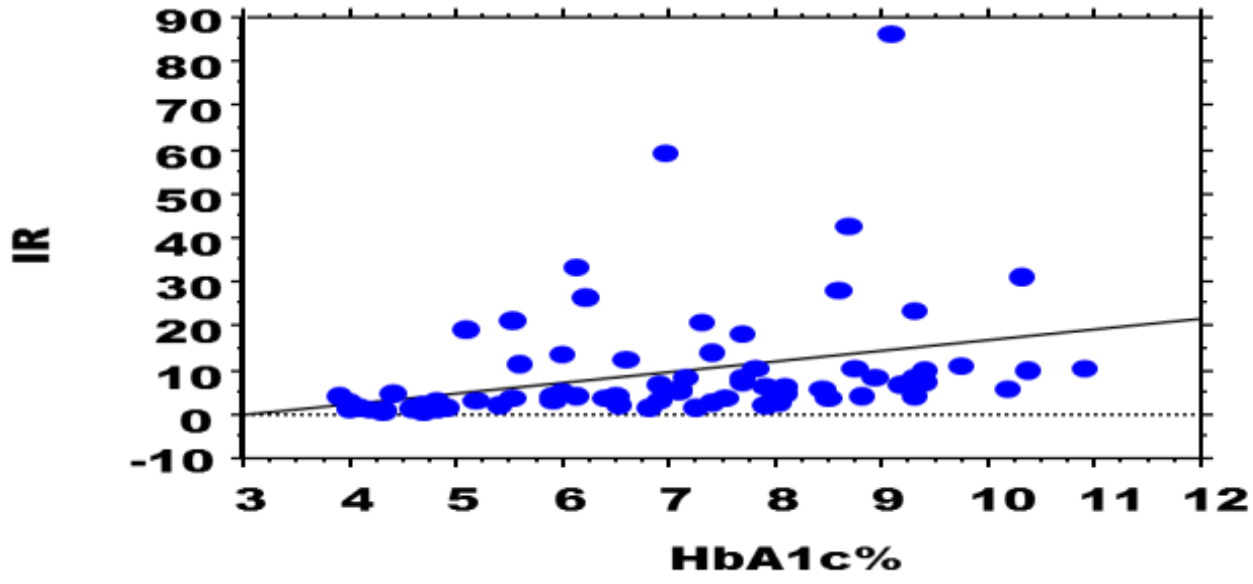

Figure 5: represents correlation between HbA1c and IR

HbA1c showed positive significant (p< 0.01) correlation (0.670) with TG; positive significant (p< 0.01) correlation (0.406) with VLDL and positive significant (p< 0.01) correlation (0.281) with BMI. Figure (6).

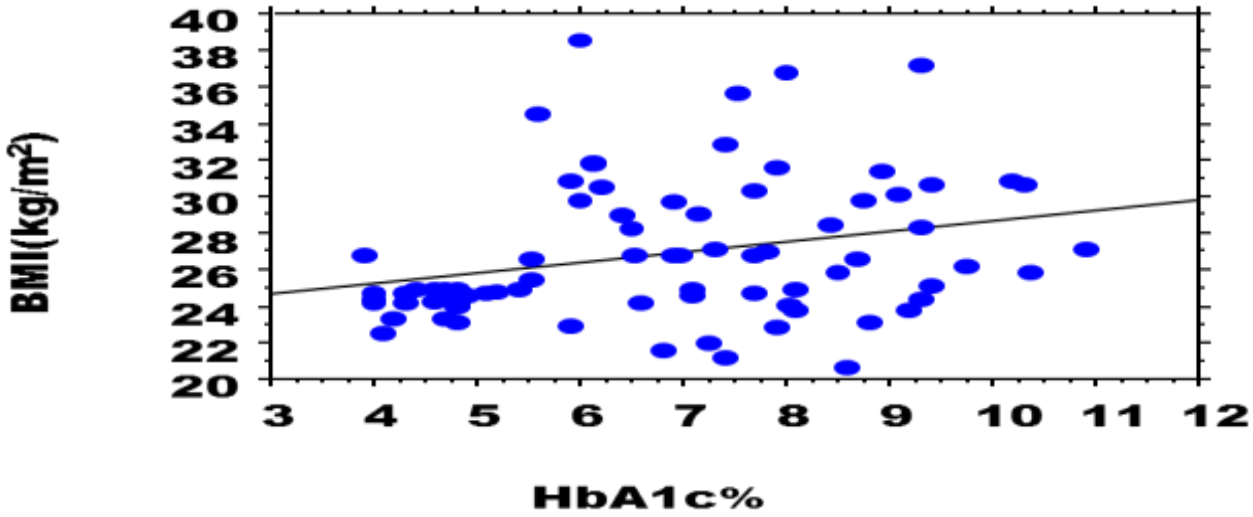

Figure 6: represents correlation between HbA1c and BMI

Table 3: Shows correlation coefficient of FBG with TG and VLDL

parameters	Correlation Coefficient of FBG	Level sig.
TG	0.545	**
VLDL	0.529	**

**P<0.01

FBG showed positive significant (p< 0.01) correlation (0.545) with TG and positive significant (p< 0.01) correlation (0.529) with VLDL.

Table 4: Shows correlation coefficient of Insulin and IR with lipid profile and BMI.

Parameters	Correlation Coefficient of			
	Insulin	Level sig.	I.R	Level sig.
TC	-0.244	*	-0.207	N.S
TG	0.134	N.S	0.244	**
LDL	-0.552	N.S	-0.327	*
VLDL	-0.134	N.S	0.238	*
HDL	-0.219	*	0.194	N.S
BMI	0.313	**	0.268	**

*P<0.05, **P<0.01, N.S=Non Significant

Insulin showed negative significant (p< 0.01) correlation (-0.244) with TC. Figure (10). Insulin showed negative significant (p< 0.05) correlation (-0.219) with HDL; and positive significant (p< 0.01) correlation (0.313) with BMI.IR showed positive significant (p< 0.05) correlation (0.244) with TG; negative significant (p<0.05) correlation (-0.327) with LDL; positive significant (p< 0.05) correlation (0.238) with VLDL; and positive significant (p< 0.01) correlation (0.268) with BMI.

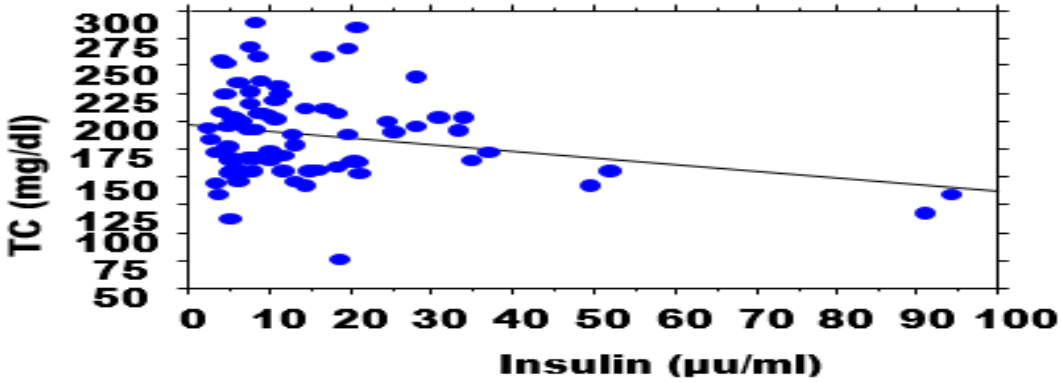

Figure 7: represents correlation between insulin and TC

Table 5: shows lipid profile (Mean ± SE) in control and diabetic groups

Groups	Mean ± SE (mg/dl)				
	TC (mg/dl)	TG (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	HDL (mg/dl)
Normal value	150-200	40-150	69-166	8-30	40-60
Control	186.40 ± 7.47	125.55 ± 11.18	111.85 ± 7.24	23.99 ± 2.47	50.46 ± 1.86
Diabetic	188.83 ± 5.46	208.05 ± 11.41	102.23 ± 4.29	41.95 ± 2.33	47.15 ± 1.15
T-Test	0.233NS	3.955 **	1.127NS	4.176 **	1.459 NS

Total cholesterol showed non-significantly (p> 0.05) difference in diabetic group (188.83 ± 5.46) in comparison with control group (186.40 ± 7.47). Triglyceride value was increased significantly (p < 0.01) in diabetic group (208.05 ± 11.41) when compared with control group (125.55 ± 11.18).Figure (8).

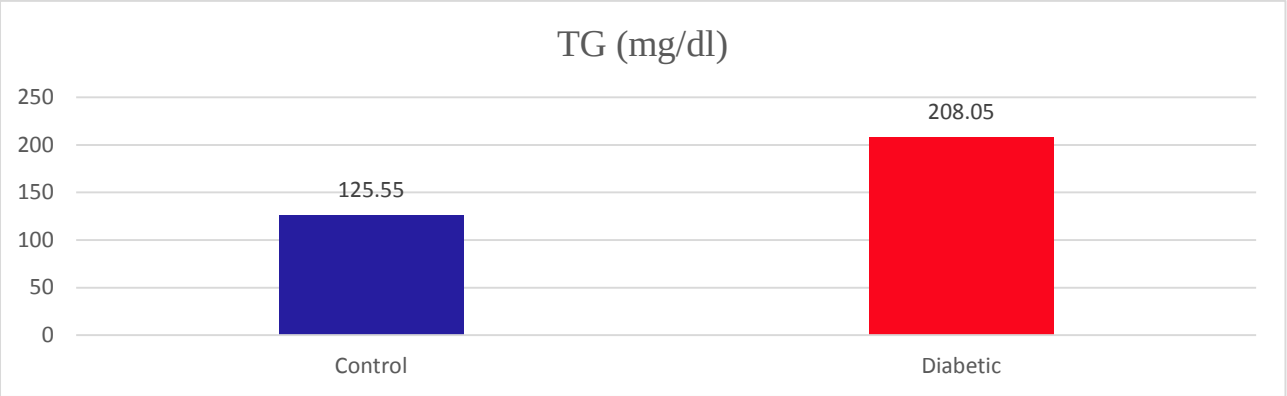

Figure 8: Represents the TG in control and diabetic groups

LDL showed non-significant (p> 0.05) difference in diabetic group (102.23 ± 4.29) in comparison with control group (111.85 ± 7.24). VLDL was increased significantly (p < 0.01) in diabetic group (41.95 ± 2.33) when compared with control group (23.99 ± 2.47). Figure (9).

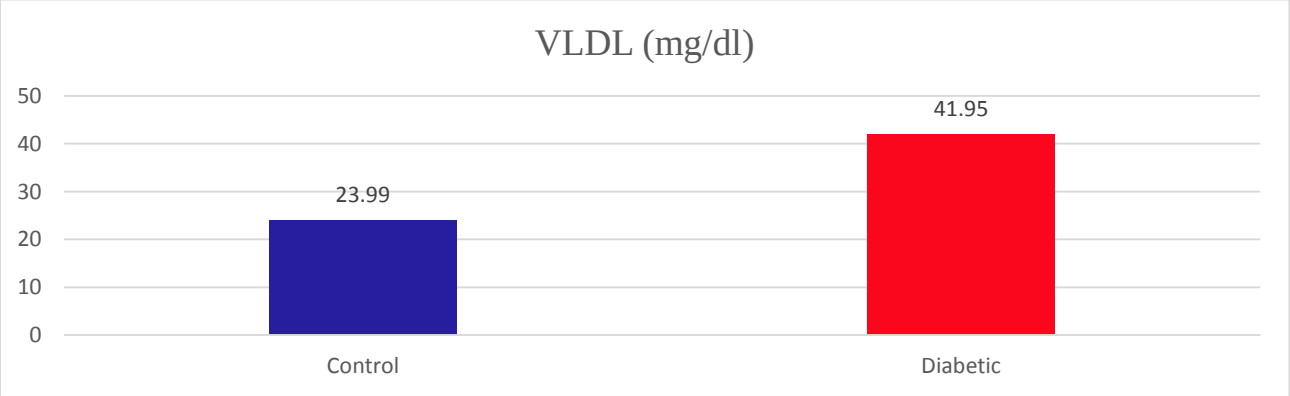

Figure 9: Represents the VLDL in control and diabetic groups

HDL showed non-significant difference (p> 0.05) in diabetic group (47.15 ± 1.15) in comparison with control group (50.46 ± 1.86). Hypertriglyceridemia (Table 2) may be caused by an increased hepatic secretion of very low-density lipoproteins (VLDL) and clearance of TG-rich lipoproteinsis delayed, which may be mainly due to elevation the substrates levels for TG production, and enhanced (FFA), and levels of glucose. The latter could be secondary to decreased activity of lipoprotein lipase (LPL), a key enzyme for lipoprotein-TG. [28]. Thus, there is a strong association between type 2 diabetes and dyslipidemia. Derangements in lipid metabolism are a driving force in the pathogenesis of insulin resistance (IR) [29]. The characteristic of lipid profile in an individual with insulin resistance includes: (1) decreased serum HDL cholesterol; [2] increased serum VLDL; and [3] less commonly, an increase in LDL cholesterol [30].The plasma VLDL concentration is determined by two factors: (1) the rate of

VLDL synthesis by the liver; and [2] the rate of VLDL removal by peripheral tissues. It is possible that insulin resistance may cause increased triglyceride concentrations. The interaction of insulin resistance with triglyceride metabolism could be either with lipoprotein lipase activity or with VLDL secretion [31].

Table 6: Shows (Mean ± SE) of IL-6 and TNF-α(pg/ml)) in control and diabetic groups

Groups	Mean ± SE	
	IL-6 (pg/ml)	TNF-α (pg/ml)
Control	4.186 ± 0.509	11.082 ± 1.204
Diabetic	9.065 ± 0.504	44.222 ± 7.336
T-Test	5.105**	2.437*

*P<0.05, **P<0.01

The IL-6 increased significantly (p< 0.01) in diabetic group (9.065 ± 0.504) in comparison with control group (4.186 ± 0.509). Figure (10).

Figure 10: Represents the IL-6in control and diabetic groups

The TNF-α showed significant increase (p< 0.05) in diabetic group (44.222 ± 7.336) in comparison with control group (11.082 ± 1.204). Figure (11).

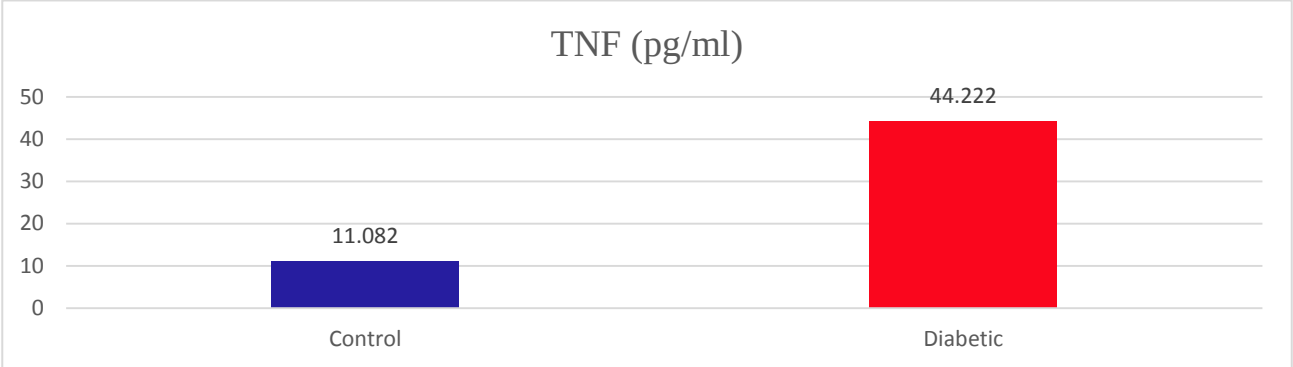

Figure 11: Represents the TNF-α in control and diabetic groups

IL-6 and TNF-α levels increased in diabetic group in comparison with control group (Table 6) that the multifunctional cytokine IL-6 is produced by the various cells involving adipocytes, endothelial cells, smooth muscle cells, fibroblasts, lymphocytes and macrophages [32,33]. Its high circulating levels has been associated with variety of diseases like obesity, diabetes and cardiovascular diseases [34].That increased serum IL-6 levels compared to normal controls might be associated with inflammation related pathophysiology in type 2 diabetes. Adipocytes secrete inflammatory cytokine, in addition they develop macrophage infiltration (adiposities) which is the source of almost all TNF–α and most of the IL-6 in adipose tissue along with other inflammatory markers [35].

Not only obesity but hyperinsulinism per se, seen in metabolic syndrome and type 2 DM, can induce rise in inflammatory markers including IL-6, TNF-α and CRP [34, 36]. Reported higher levels of IL-6 and TNF-α in 77 T2 diabetic patients in Pakistan .They found that the serum levels of IL-6 and TNF- α did not show correlation with BMI as we observed in our study, Probably the

relationship between cytokine levels and BMI is not linear.

The increase of IL-6 levels in our study in diabetic overweight BMI (27.59 ± 0.52) that adipose cells contribute 15 to 30% of circulating IL-6 levels in the absence of acute inflammation [37].Production is significantly enhanced by adipose tissue in obesity(38).IL-6 synthesis is up regulated in adipocytes in obesity and correlates to some extent of IR. IL-6 from other side triggering the hepatic synthesis of CRP and promotes hepatic VLDL secretion with hypertriglyceridemia [39].

These notices suggest a correlation between IL-6 concentrations with obesity and inflammation in the T2DM pathogenesis and showed that IL-6 can be regarded as a candidate biomarker for early foundation of T2DM risk [40]. The pathophysiology of IR and T2DM is related to the high TNF-α level, possibly through its effect on IRS-1 or by increasing the apoptosis of pancreatic ß-cells [41].

Many of the clinical biochemical features and the complications of T2DM may be explained by the augmented acute-phase response. Cytokines, mainly IL-1, IL-6 and tumor necrosis factor-alpha (TNF-α), act on the liver to produce the characteristic dyslipidaemia of T2DM (increased very low density lipoprotein [VLDL] and decreased (HDL) and may contribute to obesity, hypertension and insulin resistance [42,43,44].As we found a positive correlation of IL-6 with TC (0.3),LDL (0.298) and blood glucose(0.382).(Table 7).

That [45] reported positive correlation in 182 Chinese patients with T2DM for these TC and LDL (0.152;0.176)from the outpatient Diabetes Clinic of the Tongde Hospital in Zhejiang province, IL-6 concentrations were significantly associated with the levels of glucose, (0.382) suggesting a role of IL-6 in the process of insulin secretion under certain conditions such as high glucose concentrations. [46].

One reason for the major impact of obesity on the development of type 2 diabetes is that it often is accompanied by the metabolic syndrome, a cluster of hyperglycemia, dyslipidemia, and hypertension [47].

Table 7: shows correlation coefficient of IL-6 with FBG, TC and LDL

Parameters	Correlation Coefficient of IL-6	Level sig.
FBG	0.382	**
TC	0.3	*
LDL	0.298	*

*P<0.05, **P<0.01

IL-6 showed positive significant (p< 0.01) correlation (0.384) with FBG; positive significant (p< 0.05) correlation (0.3) with TC; and positive significant (p< 0.01) correlation (0.298) with LDL. We concluded from our present study that the increasing in the IL-6 and TNF-α levels with dyslipidemia may contribute to IR, and also circulating IL-6 levels increase in diabetes patients due to underline chronic inflammation.

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