

Comparative Analysis of Interferon-Gamma Inducible Protein-10 in Iraqi Type 2 Diabetes Mellitus Patients with and without Dyslipidemia

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ABSTRACT

Background: Hyperglycemia plays a crucial role in the development of diabetic dyslipidemia and its associated complications. Emerging evidence suggests that interferon-gamma-inducible protein-10 (IP-10) and insulin resistance (IR) are key factors contributing to metabolic disturbances in type 2 diabetes mellitus (T2DM). Understanding their role may aid in predicting cardiovascular disease risk and monitoring disease progression in diabetic patients. **Objective:** This study aimed to compare IP-10 and insulin levels among patients with T2DM, patients with both T2DM and dyslipidemia, and healthy controls to evaluate their potential as predictive biomarkers for cardiovascular complications. **Methods:** A total of 150 participants were enrolled and categorized into three groups: 50 healthy controls (G1), 50 patients with T2DM (G2), and 50 patients with T2DM and dyslipidemia (G3). Fasting glucose (FSG), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein (HDL) levels were measured using enzymatic methods. Insulin and IP-10 levels were assessed using enzyme-linked immunosorbent assay (ELISA), and glycated hemoglobin (HbA1c) was measured in whole blood. **Results:** FSG and HbA1c levels were significantly elevated in both G2 and G3 compared to G1 ($p < 0.05$). Lipid profile analysis revealed a significant increase in TG, TC, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) levels in G3 compared to both G1 and G2, while HDL levels were significantly reduced in G3 ($p < 0.05$). Insulin and IR levels were markedly higher in G2 compared to G1 and showed a further significant increase in G3 compared to G2 ($p < 0.05$). IP-10 levels exhibited a significant increase in G2 compared to G1; however, a notable decrease was observed in G3 compared to G2 ($p < 0.05$). **Conclusion:** This study is among the first to investigate the role of IP-10 in diabetic dyslipidemia and its relationship with metabolic dysfunction. The findings suggest that IP-10 may serve as a potential biomarker for predicting and monitoring the progression of dyslipidemia in T2DM patients, potentially aiding in the prevention of cardiovascular complications. Further research is needed to establish its clinical applicability in routine disease monitoring.

Keywords: Diabetes mellitus, Dyslipidemia, Iraqi, IP-10, Insulin

INTRODUCTION

A group of lipoprotein abnormalities characterized by increased triglyceride levels, reduced HDL cholesterol, and an increase in small, dense LDL (LDL) particles is known as diabetes-related dyslipidemia. In diabetic dyslipidemia, LDL cholesterol is the most important predictor of atherosclerotic and cardiovascular disease [1, 2]. IP-10 is a chemokine with 8.7 KDa protein which is secreted in response to interferon-gamma activation, T-cells, endothelial cells, monocytes, and keratinocytes [3, 4]. The IP-10 shows a strong correlation with BMI, HOMA-IR score indicating that these variables may be utilized as markers of insulin resistance. Due to its potential to prevent adipose tissue angiogenesis, IP-10 may be detrimental to metabolic disorders and obesity [5]. An anabolic hormone, insulin, affects a wide range of cell types. Insulin's primary metabolic effects include enhancing skeletal muscle and adipocyte glucose absorption, encouraging skeletal muscle glycogen synthesis, reducing hepatic glucose synthesis, and preventing adipocyte lipolysis [6]. An experimental or clinical condition known as insulin resistance is characterized by a biological action of insulin that is lower than anticipated. Since skeletal muscle, adipocytes, and liver tissue are the primary sites of intracellular glucose transport as well as glucose and lipid metabolism, insulin resistance has a substantial impact on these tissues because of their high metabolic demand [7, 8]. Present study aimed to investigate the levels of IP-10 in patients with T2DM and dyslipidemia as complication then results compared with diabetic patient group and

control. In addition, the correlation relation of IP-10 with some studied parameters examined which may be considered as a monitoring biomarker for IR and dyslipidemia in diabetic patients.

MATERIALS AND METHODS

A 150 Subjects enrolled in this study that separated into three groups. Group1 represent as control healthy individual ($n=50$). Group2 as T2DM patients without dyslipidemia ($n=50$), and group3 as T2DM patient with dyslipidemia ($n=50$). Age of subjects ranged (35-55), with BMI (kg/m^2). Blood collecting during November (2022) to April (2023). Patients diagnosed by T2DM at the National Center for Diabetes Research and treatment. Five milliliters of venous blood were collected from each subject. Whole blood was taken in order to HbA1C estimation. Serum used to determination of insulin and IP-10 levels by ELISA technique utilizing kits provided by Mybiosource (USA). The FGS, TG, TC and HDL were determined in serum by manual methods. The LDL and VLDL were calculated using the Friedewald equation. For statistical analysis, the statistical programmer SPSS-21 (Statistical Packages for Social Sciences, version 21) was used. The variables' mean and standard deviation were shown using descriptive analysis. When the P-value was equal to or less than ($p \leq 0.05$), it was considered significant. Pearson's correlation was used to establish a correlation between two quantitative variables, and the t-test was used to determine the significance of the connection. Three different groups

were examined using the Receiver Operating Characteristic (ROC) curve analysis for IP-10.

Results and Discussions

To the best of our knowledge, this is the first research to measure IP-10 levels in patients with dyslipidemia who have diabetes and compare the outcomes with those of patients with diabetes and control groups. Additionally, in these situations, the ROC research looked at IP-10 for the first time. In this research, 150 participants were split up

into 3 groups. Group 1 as a sound reference point (G1). Patients with diabetes mellitus with dyslipidemia (G3) and those with diabetes mellitus (G2) make up Group 3. They were 35 to 55 years old, and their BMI was kg/m². The values of FSG, HbA1c, TG, TC, LDL, VLD, and HDL are shown in Table 1. There was a significant rise in G2 and G3 over G1, according to the FSG and HbA1c data. Table1 illustrates the non-significant rise seen in G3 relative to G2. Numerous studies concur with the present study, which showed that diabetes patients had higher levels of FGS and HbA1c than control [9-11].

Table 1: FGS, HbA1c, T.G, T.C, HDL, LDL and VLDL levels in G1, G2&G3.

Parameter	Mean $\pm$ SD			p-value		
	G1 n=(50)	G2 n=(50)	G3 n=(50)	G1&G2	G1&G3	G2&G3
FGS(mg/dL)	88.97 $\pm$ 8.82	184.5 $\pm$ 88.41	211.5 $\pm$ 82.29	S	S	NS
HbA1c %	4.87 $\pm$ 0.43	8.53 $\pm$ 1.95	8.75 $\pm$ 1.79	S	S	NS
T.G(mg/dL)	93.47 $\pm$ 15.77	101.47 $\pm$ 33.89	237.93 $\pm$ 51.88	N.S	S	S
T.C(mg/dL)	156.07 $\pm$ 26.3	157.33 $\pm$ 33.14	216.00 $\pm$ 35.54	NS	S	S
HDL(mg/dL)	51.46 $\pm$ 7.41	46.21 $\pm$ 10.90	31.21 $\pm$ 4.45	NS	S	S
LDL(mg/dL)	87.86 $\pm$ 28.45	94.76 $\pm$ 35.46	104.93 $\pm$ 47.94	NS	S	S
VLDL(mg/dL)	18.10 $\pm$ 3.70	19.29 $\pm$ 6.85	50.93 $\pm$ 23.89	NS	S	S

G1:Control, G2:T2DM, G3:T2DM with dyslipidemia, NS: non-significant: ($p>0.05$)

Several studies have shown that individuals with diabetes have higher rates of dyslipidemia, which is linked to poor glycemic control, elevated HbA1c levels in plasma blood, and hypercholesterolemia [12-14]. Table1 findings demonstrated T.G levels, which were significantly higher in G3 (237.93) than in G1 (93.47) and G2 (101.47) ng/mL. Furthermore, a non-significant rise in G2 over G1 was observed. TC levels in G3(216) ng/mL are significantly higher than TC in G1(156.07) and G2(157.33) ng/mL. Additionally, there was a non-significant rise in G2 over G1. Table1 results also showed that G3 had significantly higher VLDL levels than G2 and G1. Although there was a significant rise in G2 and G1. In G3, HDL levels were much lower than in G2 and G1. Additionally, non-significant changes between G2 and

G1 were discovered. According to a recent study, diabetic dyslipidemia and diabetes mellitus frequently co-occur [15, 16]. Diabetes's increased CV risk is mostly mediated by dyslipidemia. Hyperglycemia may be the result of, or perhaps the source of, hypertriglyceridemia and low c-HDL because they can both cause abnormalities in how glucose is metabolized [17, 18].

Levels of Insulin and Insulin Resistance (IR)

Table2 displays IP-10, insulin, and IR values for each group under study. The G2 and G3 significantly increased in comparison to G1 based on insulin and IR results. Furthermore, a significant rise in G3 relative to G2 was observed.

Table 2: Insulin, I.R and IP-10 levels in G1, G2&G3

Parameter	Mean $\pm$ SD			p-value		
	G1 n=(50)	G2 n=(50)	G3 n=(50)	G1&G2	G1&G3	G2&G3
Insulin (pg/ml)	76.22 $\pm$ 10.26	170.28 $\pm$ 46.84	245.86 $\pm$ 36.22	S	S	S
IR	0.266 $\pm$ 0.035	0.599 $\pm$ 0.162	0.863 $\pm$ 0.129	S	S	S
IP-10 (pg/ml)	149.5 $\pm$ 25.98	229.79 $\pm$ 64.93	207.63 $\pm$ 22.60	S	S	S

G1: Control, G2:T2DM, G3:T2DM with dyslipidemia, NS: non-significant: ($p>0.05$)

A major lipoprotein anomaly thought to characterize diabetic dyslipidemia is the overproduction of VLDL1 particles, which encourages the production of sdLDL particles and lowers HDL-C levels. VLDL1-TG level is the main indicator of LDL Size, and the production of sdLDL is tightly correlated with resistance to insulin and hypertriglyceridemia [19]. A recent study indicated that insulin was higher in the groups with diabetes than in the control group, which may be related to those patients' increased insulin resistance [20]. Results is agreement with current study. A research found that subclinical inflammation raises the risk of type 2 diabetes and causes insulin resistance, which is connected to metabolic syndrome symptoms [12].

Apart from impairing insulin signaling on important intimal cells (endothelium, smooth muscle cells of the vascular system, and macrophages), insulin resistance also encourages a state of pro-inflammatory and dyslipidemia, which, in conjunction with hyperinsulinemia, leads to an acceleration of plaque formation [21]. Table2 results demonstrated that, in comparison to G1, IP-10 levels were significantly higher in G2 and G3. However, there was a significant drop in G3 as opposed to G2. The expression of the IP-10 gene is negatively correlated with markers of dyslipidemia which is

lower in dyslipidemia patients [22]. Using ordinal logistic regression analysis, the IP-10 was shown to be an independent risk factor for the development of diabetes, insulin resistance, and progressive liver damage. In relation to IP-10 and type 2 diabetes, a previous population-based study revealed that there was noteworthy increase in IP-10 in individuals with type 2 diabetes relative to control participants [23]. Study's reported the relationship between a cohort of type 2 diabetes (T2D) patients' plasma levels of the chemokine IP-10 and the presence of DPN [24]. Additionally, it has been proposed that chemokine IP-10 may serve as a biomarker for angiogenesis and inflammation in T2D patients. There has been information on a correlation between IP-10 and heart attacks or strokes. These findings point to an independent function for IP-10 in heart failure and mortality risk from C-reactive protein [25]. Various cell types, such as T lymphocytes, neutrophils, endothelial cells, monocytes, and fibroblasts, release IP-10. The attraction of T cells and monocytes, control over angiogenesis, and development of naïve T cells into pro-inflammatory T helper 1 cells are some of these effects [26, 27].

Correlation Study of IP-10 with Insulin, TG and TC

Table 3 shows the IP-10 correlation coefficient (r) and P-value with insulin, TG and TC for G1, G2, and G3.

Table 3: The r value and p-value of IP-10 with insulin, TG and TC for G1, G2 and G3.

Parameters	G1	G2	G3
Insulin	$r_1 = 0.346$ p-value N.S	$r_2 = -0.108$ p-value S	$r_3 = -0.194$ p-value S
T.G	$r_1 = 0.289$ p-value N.S	$r_2 = -0.188$ p-value S	$r_3 = -0.262$ p-value S
T.C	$r_1 = -0.044$ p-value N.S	$r_2 = -0.262$ p-value S	$r_3 = -0.260$ p-value S

G1: Control, G2:T2DM, G3:T2DM with dyslipidemia, NS: non-significant: ($p > 0.05$)

A positive non-significant correlation relation (r) in G1 is shown by the data in Table 3 and Fig. 1 ($r_1 = 0.346$). Conversely, IP-10 with

Insulin, a negative significant correlation association was seen in G2 ($r_2 = -0.108$) and G3 ($r_3 = -0.194$).

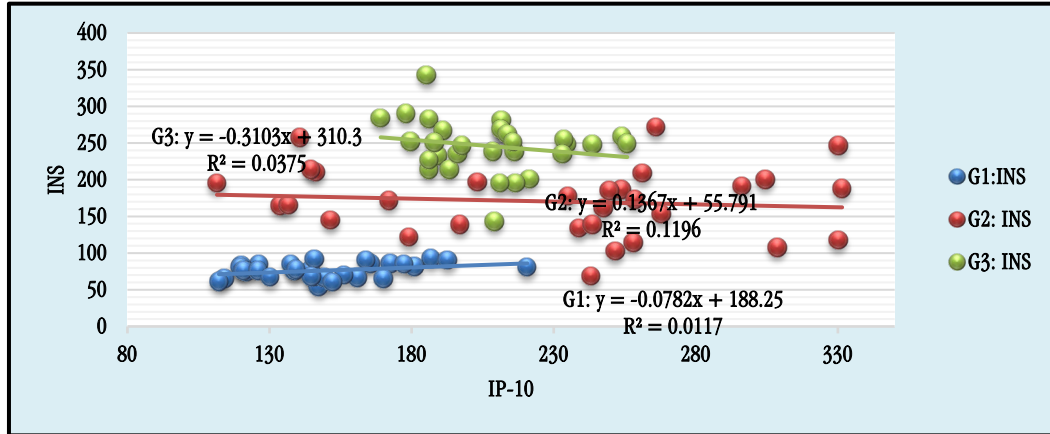


Figure 1: Correlation relation of IP-10 with Insulin in G1, G2 and G3.

A positive non-significant correlation relation in G1 ($r = 0.289$) were noticed, while a negative significant correlation relation was found in G2 ($r_2 = -0.188$) and G3 ($r_3 = -0.262$) for IP-10 with T.G, as shown

in Fig.2. A negative non-significant correlation relation in G1 ($r = -0.044$) was found. While a significant r value found in G2 ($r_2 = -0.262$), and G3 ($r_3 = -0.260$) for IP-10 with T.C, as shown in Fig.3.

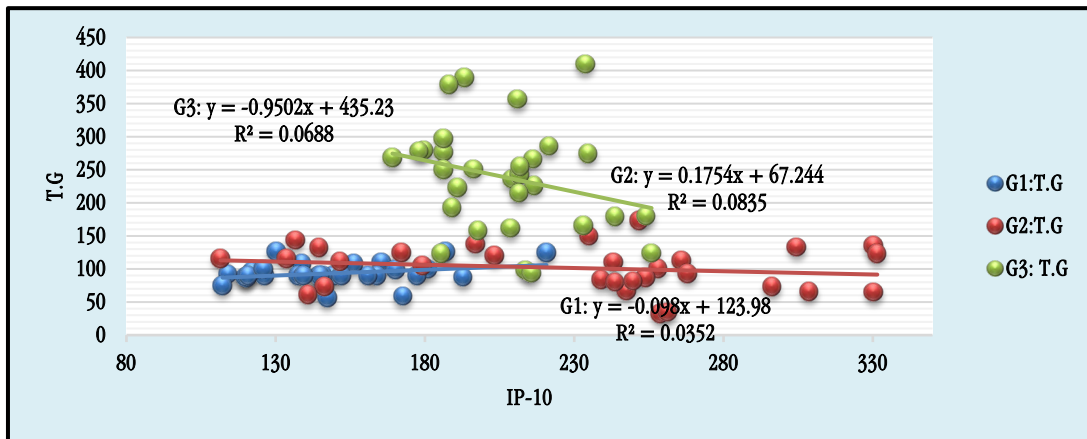


Figure 2: Correlation Relation of IP-10 with T.G in G1, G2 and G3.

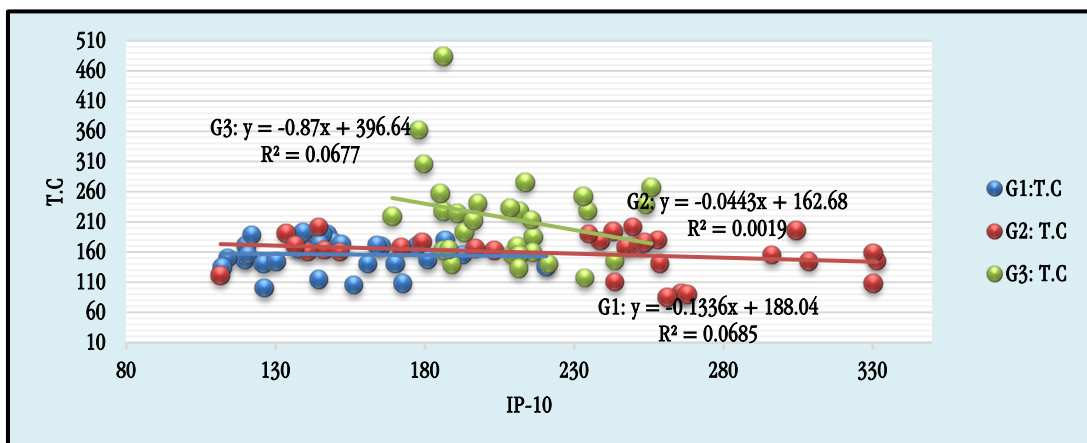


Figure 3: Correlation Relation of IP-10 with T.C in G1, G2 and G3.

Roc study of IP-10:

The examination of the Receiver Operating Characteristic (ROC) curve for IP-10 in three different groups shows an excellent 0.67 area under the curve (AUC). The p-value of 0.0048, which is less than the threshold of 0.01, indicates that this AUC value is statistically significant at a 95% confidence level.

The optimal cut-off value for IP-10 is determined to be 177.45, with a sensitivity of 74% and a specificity of 64%. This suggests a high level of accuracy in distinguishing between the groups. These findings are graphically represented in Table 4 and Fig. 4, which visually illustrates the robustness and efficacy of the IP-10 test across the groups.

Table 4: Difference between sensitivity and specificity for IP-10.

Variables	Sensitivity	Specificity	Area under the curve	Accuracy	L.B.	U.B.	Cut off value
IP-10	0.74	0.64	0.67	0.55		0.78	177.45

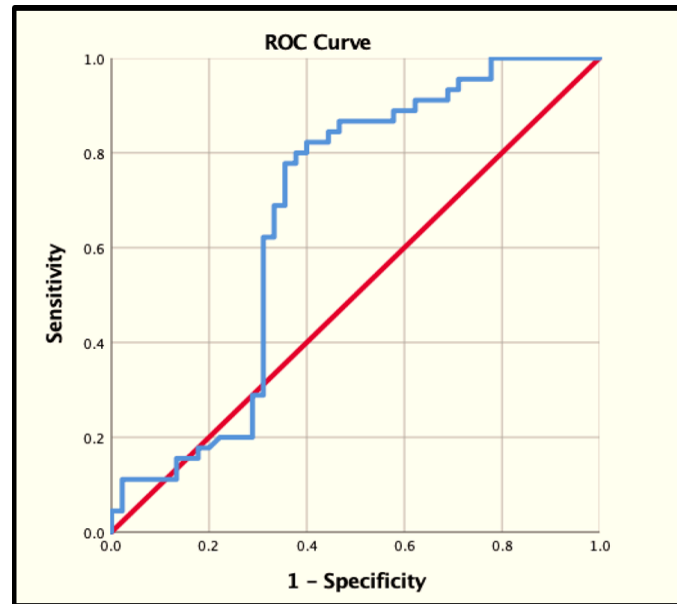


Figure 4: ROC Curve for IP-10

Conclusion

Results of current study revealed that IP-10 could be considered diagnostic marker in T2DM patients to identify the first stages of dyslipidemia.

Correlation of IP-10 with Insulin in DM patients, may be used as a prognostic indicator to foretell the development of DM and dyslipidemia. In addition, ROC study improved that IP-10 perfect test might help diabetic patients better categorize their risk of developing

dyslipidemia and other problems. Further research is needed to investigate role of IP-10 in diabetic dyslipidemia patients.

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