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A Study of the Association Between IL-17 and HOMA-IR in Iraqi Type 2 Diabetic Patients

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Abstract

Type 2 Diabetes Mellitus (T2DM) is the furthermost common form of DM which is identified by hyperglycemia, insulin resistance, and relative insulin deficiency. This study aims to detect the role of interleukin-17 (IL-17) in patients with T2DM compared with the healthy control and to investigate the relationship between IL-17 and insulin resistance. The study involved 50 Iraqi T2DM patients, randomly selected with an age range of 33-71 years .For the purpose of comparison, 30 Iraqi healthy persons with an age range of 33-71 years were also included. Patients and control groups were characterized in terms of gender, age, body mass index (BMI), homeostatic model assessment-insulin resistance(HOMA-IR),fasting serum glucose (FSG) and lipid profile. The means of IL-17 (368.45 vs. 128.50 pg/ml), HOMA-IR (7.94vs. 2.14),FSG (152.82 vs. 81.53 mg/dl), fasting serum insulin (FSI) level (19.37 vs. 10.71 μ IU/ml), Triglycerides (TG), High Density Lipoprotein (HDL),and Very Low Density Lipoprotein (VLDL) were significantly higher in T2DM patients as compared to controls. While, levels of Total Cholesterol (TC)and Low Density Lipoprotein (LDL)showed non-significant differences. In conclusion, IL-17 seems to play a significant role as a risk factor for the development of T2DM.Also, higher (HOMA-IR) gives rise to a hyperglycemic state and is a major risk factor for the development of T2DM.

Keywords: Interleukin-17, T2DM, HOMA-IR, lipid profile.

دراسة العلاقة الترابطية بين الإنترلوكين 17 ومقاومة الأنسولين لدى مرضى السكري العراقيين النوع

الثاني

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الخلاصة

داء السكري من النوع الثاني (T2DM) هو النوع الأكثر شيوعاً لمرض السكري الذي يتم تمييزه من خلال ارتفاع السكر في الدم ومقاومة الأنسولين ونقص الأنسولين النسبي. تهدف الدراسة إلى كشف دور إنترلوكين 17 (IL-17) في المرضى الذين يعانون من داء السكري النوع الثاني مقارنة مع مجموعة من

الإصحاء ، أيضًا ، لاستقصاء العلاقة بين انترلوكين 17 ومقاومة الأنسولين. شملت الدراسة 50 مريضاً عراقياً من مرضى السكري النوع الثاني ، تم اختيارهم بمعدل عمر يتراوح من 33 - 71 سنة تم اختيارهم عشوائياً ، ولغرض المقارنة ، تم إدراج 30 شخصاً عراقياً أصحاء ، وايضاً بمعدل عمر يتراوح من 33 - 71 سنة. تميز المرضى ومجموعة السيطرة بالتوافق من حيث الجنس والعمر ومؤشر كتلة الجسم (BMI) ، ومعادلة تقييم نموذج الأنسولين (HOMA-IR) ، ومصل سكر الصيام (FSG) وملف الدهون. المتوسط الحسابي للانترلوكين 17 (368.45 مقابل 128.50 جزء من الغرام / مل) ،معادلة تقييم نموذج الأنسولين (HOMA-IR) (7.94مقابل 2.14) ، ومصل سكر الصيام (FSG) (152.82 مقابل 81.53 ملغ / دل) ، مستوى الأنسولين في مصل الصيام (19.37 مقابل 10.71 $\mu\text{U} / \text{ml}$) ، والدهون الثلاثية (TG) ، البروتين الدهني عالي الكثافة (HDL) ، والبروتين الدهني منخفض الكثافة جدا (VLDL) كانت زيادة معنوية في مرضى السكري النوع الثاني بالمقارنة مع مجموعة السيطرة . بينما الكوليسترول الكلي (TC) والبروتين الدهني منخفض الكثافة (LDL) اظهرت عدم وجود فروق معنوية في مجموعة المرضى مقارنة بمجموعة الإصحاء. يلعب انترلوكين 17 دوراً مهماً كعامل خطورة في تطور مرض السكري النوع الثاني ، كما أن زيادة مقاومة الانسولين (HOMA-IR) تؤدي إلى حالة ارتفاع السكر في الدم هو عامل خطورة رئيسي لتطور داء السكري النوع الثاني.

Introduction

Type 2 Diabetes Mellitus (T2DM) is the furthestmost common form of DM which is identified via hyperglycemia, insulin resistance, and relative insulin deficiency [1]. T2DM represents approximately 90% of all types of diabetes. In T2D, hyperglycaemia is the outcome of insufficient production of insulin and inability of the body to react fully to insulin, a case that is well-defined as insulin resistance [2]. The risk of developing T2DM rises with obesity, age, and physical inactivity. It occurs more recurrently in those with dyslipidemia or hypertension [3]. It was appraised that in 2017 there were 451 million (age 18–99 years) individuals with diabetes worldwide [4]. The prevalence of T2D in Iraq reached epidemical proportions in 2007, impacting about 2 million people or 7.43% of the total Iraqi population [5].

Interleukin-17 (IL-17) is a pro-inflammatory cytokine secreted via activated T-cells, which produces an immune response to exogenous fungal and bacterial pathogens and plays a role in the development of inflammatory and autoimmune diseases [6]. IL-17A, also called IL17, is the most important IL from the IL17 family which comprises 6 members (IL17A→IL17F). IL17 is produced by T helper 17 cells and contributes to both acquired and innate immune responses against exogenous pathogens. The roles of Th17 and its cytokines (IL17 and 22) have been recognized in inflamed tissues in different autoimmune diseases[7]. IL-17 acts on a broad range of cells such as endothelial cells, fibroblasts, keratinocytes and macrophages, promoting the expression of cytokines(IL-1, TNF, and IL-6), metalloproteinases and chemokines[8]. There is a correlation between the existence of pro-inflammatory adipose tissue macrophage (M1ATM) and CD4+ Th17 cells in obese adipose tissue (AT). Thus, IL-6, IL-1 β , and IL-23, which are produced by M1 ATM, have been linked with the expansion and declension of Th17 cells in obese and T2D patients[9].

Insulin resistance (IR) is known as an impaired biologic response to insulin stimulation of target tissues, predominantly liver, adipose tissue, and muscles. IR impairs glucose disposal, causing a compensatory rise in beta-cell insulin production and hyperinsulinemia[10]. IR cause impaired protein catabolism and glycogen synthesis in skeletal muscles and inhibit lipoprotein lipase activity in adipocytes leading to an increased release of free fatty acids and inflammatory cytokines such as IL-6, TNF α , and leptin. Additionally, the liver accounts for 30% of insulin-stimulated glucose disposal and insulin resistance leads to impaired glucose output and fatty acid metabolism leading to increased triglyceride content and VLDL secretion from liver [11]. This study aims to detect the role of IL-17 in patients with T2DM and to investigate the relationship between IL-17 and insulin resistance.

Material and Methods

A total of 50 Iraqi T2DM patients, 30 females and 20 males with an age range of 33-71 years, were randomly selected from those attending the National Diabetes Center for Treatment and Research at Al-Mustansiriyah University (Baghdad- Iraq) from February – May 2018. The diagnosis of T2DM was performed on the basis of the recommended criteria by WHO (2006).

For the purpose of comparisons, 30 Iraqi control subjects who were comparable to the diabetes mellitus patients in respect to age (33-72 year) and gender (17 females and 13 males) were included. Control and patients were characterized in terms of gender, age, BMI, family history of diabetes, HOMA- IR, W/H, lipid profile and FSG.

From each subject, 5 mL of blood was collected by venipuncture after 10–12 hours of fasting between 9:00 P.M. and 11:00 A.M. Blood was transferred into gel plain tubes and left to coagulate for 30 min at room temperature, then serum was collected after centrifugation at 3000 xg for 10 min. The collected serum was divided into two parts; the first part was used for the biochemical assays, whereas the second part was frozen at -20 c° in Eppendorf tubes until use.

Serum concentrations of IL-17 and Insulin were assayed by enzyme- linked Immunoabsorbant assays (ELISA) according to the manufacturer's procedures (elabscienceUSA and Monobind Inc. USA, respectively).

Total cholesterol was determined by enzymatic hydrolysis and oxidation while Triglycerides concentration was determined using enzymatic colorimetric test (Biolabo kit triglycerides – France). Total cholesterol, triglycerides and HDL were assayed by commercial kits. LDL was calculated using Friedwald's formula.

BMI was measured by dividing weight (kilograms) by the square height (meter), whereas HOMA-IR was calculated by the following equation:

$$\text{HOMA-IR} = (\text{FSI} \times \text{FSG}) / 22.5$$

where FSG is expressed with mg/dL and FSI by $\mu\text{IU} / \text{mL}$ units [12].

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences-version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference of different means (quantitative data) was tested using Students t-test for difference between two independent means or Paired t-test for difference of paired observations (or two dependent means). Statistical significance was considered whenever the p- value was less than 0.05.

Results

The mean values of FSG (152.82 vs. 81.53 mg/dL), FSI (19.37 vs. 10.71 $\mu\text{IU}/\text{mL}$), HOMA-IR (7.94 vs. 2.14), and IL-17 (368.45 vs. 128.50 pg/mL) were significantly higher in T2DM patients as compared to the controls (Table-1).

Table 1-Means of FSG, FSI, HOMA-IR, IL-17 and W/H in T2DM patients and controls

Parameter	Mean±SE (Range)		P value ≤
	Patients (n=50)	Controls (n=30)	
FSG (mg / dL)	152.82±70.58	81.53±7.43	0.0001
FSI ($\mu\text{IU}/\text{mL}$)	19.37±17.29	10.71±5.77	0.010
HOMA-IR	7.94±9.33	2.14±1.24	0.001
IL-17 (pg/mL)	368.45±311.86	128.50±98.80	0.0001

Results of total Cholesterol, TG, HDL, LDL, and VLDL of the control and patient groups are listed in Table-2. Our results showed significantly higher levels of TG, HDL and VLDL in the patients group in comparison with the controls group (p= 0.0001, 0.005, and 0.0001, respectively), while levels of TC and LDL showed non-significant differences (p= 0.748 and 0.692, respectively).

Table 2-Lipid profile levels in the control and T2DM patient groups

Parameter	Mean±SE (Range)		P value ≤
	Patients (n=50)	Controls (n=30)	
TC (mg / dL)	158.40±31.32	160.60±34.56	N.S 0.748
TG (mg / dL)	140.76±69.09	78.79±44.51	0.0001

HDL-C (mg / dL)	37.21±7.85	44.18±14.70	0.005
LDL-C (mg / dL)	95.28±27.16	98.00±38.57	N.S 0.692
VLDL-C (mg / dL)	28.12±13.92	15.70±8.91	0.0001

As shown in Table-3, only the levels of FSG and FSI showed positive significant linear correlations with HOMA-IR in patient and control groups.

Table 3-The correlation coefficient of HOMA-IR with a set of selected parameters for all subjects

		HOMA-IR		
		Diabetics (n=50)		Controls (n=30)
FSG	(mg/dL)	r	0.424	0.432
		P	0.002	0.017
FSI	(μIU/mL)	r	0.937	0.972
		P	0.0001	0.000
IL-17	(pg/mL)	r	0.259	0.141
		P	0.069	0.458

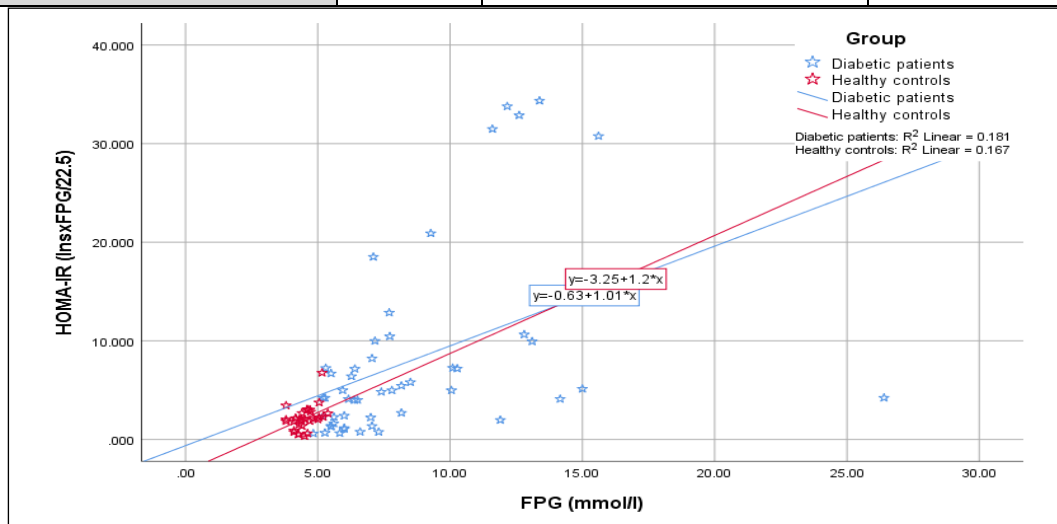


Figure 1-The correlation coefficient of HOMA-IR with FSG for all subjects

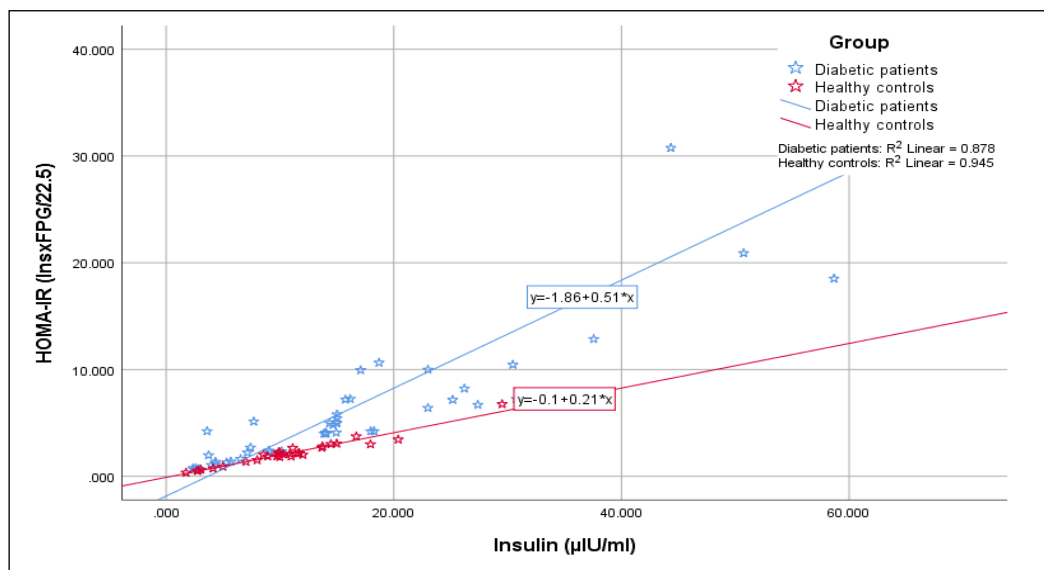


Figure 2-The correlation coefficient of HOMA-IR with FSI for all subjects.

From Table-4, it is clear that only the levels of TG and VLDL showed positive significant linear correlations with IL-17 inpatient and control groups.

Table 4-The correlation coefficient of IL-17 with a set of selected parameters for all subjects

	IL-17 (pg/ml)		
		Diabetics (n=50)	Controls (n=30)
Triglycerides (mg/dL)	r	0.404	0.577
	P	0.004	0.001
VLDL (mg/dL)	r	0.401	0.563
	P	0.004	0.001

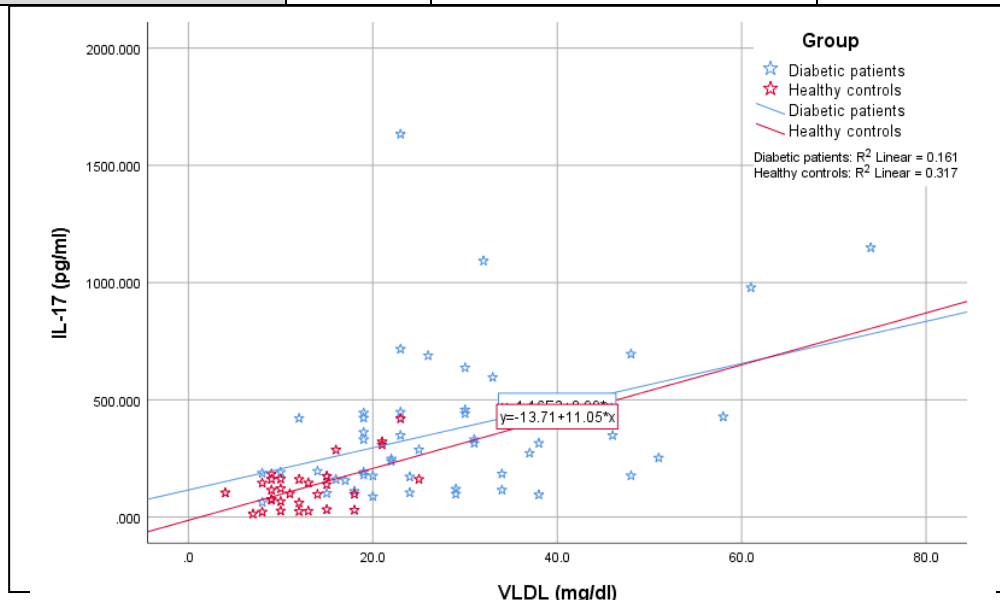


Figure 3-The correlation coefficient of IL-17 with TG for all subjects.

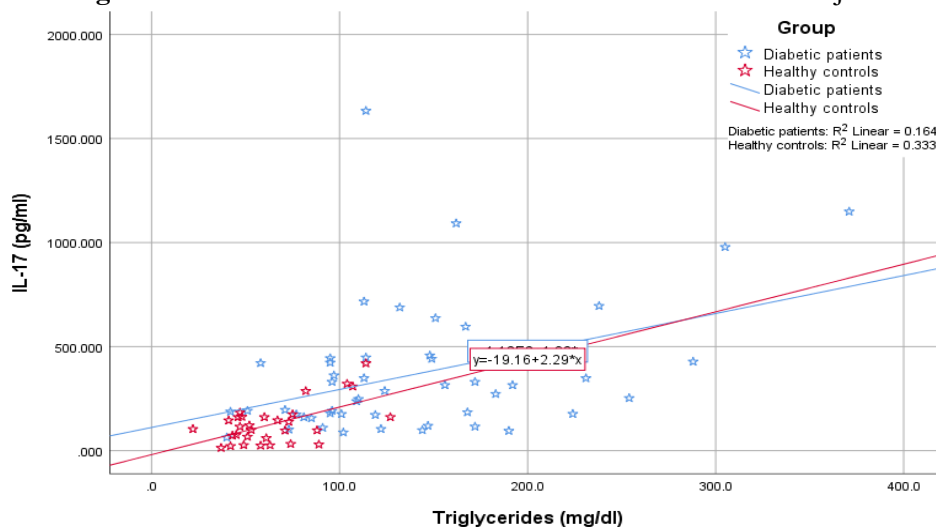


Figure 4-The correlation coefficient of IL-17 with VLDL for all subjects.

Discussion

Our present study demonstrated significantly higher levels of FSG, FSI, HOMA-IR, IL-17, W/H, TG, HDL and VLDL in T2DM patients when compared with control subjects. T2DM usually displays hyperglycemia due to the impaired response to insulin, β -cell dysfunction, and the reduced blood sugar control, indicating the role of hyperglycemia in the elevation of inflammatory injury in diabetes patients [13]. IR denotes a state in which cells of the peripheral tissue have a lowered level of response to insulin, a hormone secreted by β cells of pancreas to maintain normal levels of blood glucose. As a result, a large amount of insulin is produced, which leads to chronic hyperinsulinemia [14]. These results are in agreement with Al-Hakeim and Abdulzahra [15].

IR precedes and strongly predicts the development of T2DM and its estimation IR has been helpful in the detection of early complications and selecting the treatment options. In addition, a high score of HOMA-IR is associated with increased risk of diabetic neuropathy, retinopathy, coronary artery disease (CAD), nephropathy, and peripheral vascular disease [16].

Indeed, obesity-induced adipose tissue inflammation is the key process causing the activation of pro-inflammatory pathways that are known to inhibit insulin signaling and induce insulin resistance. On the other hand, activation of inflammatory pathways in adipocytes impairs triglyceride storage and increases the release of free fatty acids (FFAs), an excess of which is known to induce IR in muscles and liver [17]. The increase in pro-inflammatory cytokine production has been recognized as an important marker of obesity and the accompanying metabolic changes [18].

IL-17 has been implicated in the pathogenesis of inflammatory conditions, and it has been shown that the blood level of IL-17 increases in obesity [19]. Chen *et al.*, 2016 reported that IL-17 might participate in the pathogenesis of T2DM together with other inflammation cytokines [20]. Therefore, it is possible that IL-17 might participate in the local inflammation and results in the destruction of β cells in the pancreas in synergy with these inflammation cytokines [21].

W/H has been utilized as measures of central obesity (where visceral adipose tissue is stored), while BMI (kg/m²) has been utilized as a measure of general obesity [22, 23]. Central obesity has been linked with decreased glucose tolerance, adjustments in glucose - insulin homeostasis, downgraded metabolic clearance of insulin, and reduced insulin-stimulated glucose disposal [24].

The current results show lower mean levels of TC and LDL in the patients group in comparison to the control group, owing to the fact that most of T2DM patients in our study were treated with statins. The 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more commonly referred to as statins, are a class of cholesterol-lowering agents used for the treatment of dyslipidemia. Through inhibition of HMG-CoA reductase, statins ultimately prevent the endogenous production of cholesterol. Additionally, the resultant reduction in cholesterol concentration within hepatocytes triggers up-regulation of low-density lipoprotein (LDL)-receptor expression, which promotes the uptake of LDL and LDL-precursors from the systemic circulation [25].

The state of hypertriglyceridemia is of a considerable anxiety from a clinical point of view as this combination can more lead to dysregulation in glucose metabolism via inducing IR and beta - cell dysfunction [26].

The present study is consistent with Dixit *et al.*, (2014) and Ozder (2014) who reported that hypertriglyceridemia may be due to the increased hepatic secretion of VLDL and delayed clearance of TG rich lipoproteins, which is predominantly due to increased levels of substrates for TG production, FFAs and glucose [27].

Lipoprotein lipase (LPL) activity is considered the rate-limiting step of very-low-density lipoprotein triglycerides (VLDL-TG) tissue storage, and has been suggested to relate to the development of obesity as well as IR and T2D [28]. There is increasing evidence that fat distribution, especially in the abdominal area, is correlated with the most severe state of IR. Obesity in general and visceral obesity, in particular, is considered as the most important factor for the causation of IR [29].

This study shows a weak positive correlation of HOMA-IR with FSG, along with a strong positive correlation of HOMA-IR with FSI, in T2DM patient and the control groups.

IL-17 was shown to promote antiadipogenic responses and IR in adipocytes that are likely to contribute to the development of T2D in obese subjects [30]. Our results showed that there was a weak positive correlation of serum level of IL-17 with TG and VLDL in T2DM patient and the control groups.

A previous study reported that elevated serum levels of IL-17, TG, and VLDL may play a role in the development of endothelial damage and vascular dysfunction, then causing systemic inflammation and endothelial dysfunction and may be involved in the pathogenesis of DM [31].

Conclusions

Increased HOMA-IR gives rise to a hyperglycemic state and is a major risk factor for the development of T2DM. A higher significant increase in the serum level of TG and VLDL has been found in T2DM patients compared with controls. From our results, we can conclude that obesity is a risk factor to the development of T2DM. IL-17 has been shown to promote antiadipogenic responses and IR in adipocytes, likely contributing to the development of T2D in obese subjects. Also, a higher value of W/H has been found in T2DM patients compared with the controls.

We can conclude that the visceral adipose tissue and IL-17 are risk factors for the development of T2DM via their implications in the pathogenesis of inflammatory conditions.

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