Article

Production of Interleukin-11 and Interleukin-17 in Type 2 Diabetics During Treatment with AntiHyperglycemic Drugs

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Abreact

Background: Nearly 90 to 95 % of individual who suffer from diabetes have type 2 diabetes mellitus (T2DM). Generally, the body can generate the insulin in this type of diabetes, but it is failed in secretion the proper amount of insulin. This type of diabetes previously included insulin independent diabetes, or adult-onset diabetes. It is often resistant to the action of insulin, and caused by insulin resistance in the liver and skeletal muscle, increasing glucose production in the liver, over production of free fatty acids by fat cells and relative insulin deficiency.**Materials:**ninety participants were included in the current study, depending on their health status, participants were classified into 70 patients with type 2 diabetes and 20 healthy control groups.Colorimetric method was applied for measuring glucose, and sandwich-ELISA method was applied to evaluate insulin, interleukin-11 and interleukin-17 in the study samples.**Results:**the study showed that there were significant differences (p=0.000) in the glucose levels when comparing the three disease groups with the control group, moreover; the study showed that there were no significant differences when comparing between the sexes in one group (regardless of the health status of the group members).the study indicated that there were significant differences when comparing the HOMA-IR ratios of the three disease groups with the control group, while the statistical differences in the QUICKI ratios were limited for comparing the control group to both G1 (p=0.039) and G2 (p=0.015), respectively. The study revealed that there were statistically significant differences when comparing HOMA-IR ratio of the females in G1 with their peers in the control group (p=0.047), as well as when comparing the males of the second (p=0.046) and third groups (p=0.018) with their counterparts of the same sex in the control group. The statistical analysis of the showed the absence of significant differences when comparing the groups with diabetes with each other or with the control group, except the observed result of a significant decrease in the concentration of interleukin-11 in the third group compared to the control group. Results showed that there was no statistical significance when comparing the levels of interleukin-17 in the three disease groups with each other, as well as, when comparing them with the healthy group. Although the present study illustrated elevated interleukin-17 level (65.519 pg/mL) in the sample of 52 years old diabetic female patient in G2, but the study showed that levels of interleukin-17of the diabetic patients were closed to what was

noted in the control group. Results of the present study showed that there were statistically significant differences between males and females of G1 only among the groups participating in the current work, as the levels of interleukin-17 witnessed an increase in interleukin-17 concentrations of female samples compared to males. The results also showed that there were clear significant differences between females of G1 and their counterparts in G2 (p=0.043) and G3 (p=0.002), as well as females of the healthy group (p=0.001). Moreover, it has been observed that the high levels of interleukin-17 in diabetic female patients caused by reduction in the insulin production, which means that interleukin-17 elevation is associated with a defect in β-cells, exclusively in women. the current study indicated that there were excellent positive correlations between interleukin-11 and insulin in G1 (r=0.451 at p=0.046), G2 (r=0.517 at p=0.020), and the healthy group (r=0.674 at p=0.001). With the same manner, there was a high positive correlation between interleukin-11 and HOMA-IR in both G2 (r=0.595 at p=0.006) and control individuals (r=0.645 at p=0.002). On the contrary, there was a negative correlation between interleukin-11 and QUICKI (r=-0.541 at p=0.014) in the control group only. The positive relationship between interleukin-17 and insulin (r=0.490 at p=0.028) in members of G1, as well as a negative relationship was observed between interleukin-17 and QUICKI (r=-0.379 at p=0.039) in G3. A significant positive correlation between interleukin-17 and interleukin-11 (~70%, at p=0.033) was shown in G1 only.**Conclusions:** Type 2 diabetes is not linked to one sex or another or one age, but the most common age group for symptoms of the disease to appear are individuals in the fifth and sixth decades. Receiving diabetes treatments in general does not return blood sugar levels to normal limits. During insulin resistance progresses, there will be a decline in the production of anti-inflammatory proteins, including interleukin-11. Interleukin-17 is a good parameter for evaluating the T2DM patients respond to treatment in the three disease groups, regardless of the type of treatment used.

Key Words:Interleukin-11,Interleukin-17, T2DM, Anti Hyperglycemic Drugs

Introduction

Diabetes mellitus is a set of metabolic disease with glucose is not sufficiently absorbed by the skeletal muscle cells and adipocytes for energy when blood glucose levels are high, this can occur because the pancreas fails to produce sufficient insulin due to beta cell dysfunction or the insulin receptors on the skeletal muscle cells and adipocytes do not respond to the insulin resulting in abnormally high glucose levels in the blood[1]. The inability of these cells to take in glucose, their main energy source, can lead to potentially serious consequences. Hyperglycemia is accompanied by a range of long-term diseases, dysfunction and failure of various organs, especially the heart, eyes, blood vessels, kidneys and nerves[1].The problem of diabetes mellitus is increasing at world level, it is common for both genders. The main factors responsible for this worldwide problem are genetic disorder, behavioral and

environmental risk factors. The modifiable risk factors such as obesity and physical inactivity are the main non-genetic determinants of diabetes[2].

Interleukin-11 is one of the pleotropic cytokines. Interleukin-11 is classified in the interleukin-6 family and is a cytokine that shares the glycoprotein signaling receptor subunit 130, in association with its own cytokine-like receptors. Interleukin-11 has been discovered in bone marrow-derived stromal cell lines, has been found to support the growth of hematopoietic cells and adipocytes, and has been found to stimulate cell growth. The initial characterization of interleukin-11 was that it was a hematopoietic and platelet-forming cytokine, which was found to increase naturally *in vivo* with age. This serendipitous discovery led to the development of recombinant human interleukin-11 for the treatment of thrombocytopenia in chemotherapy patients. It was reported in 1996 that recombinant human interleukin-11 induced bone marrow fibrosis (myelofibrosis) in 60% of patients within 2 weeks of treatment. Increased interleukin-11 production in humans is interesting, as one of the recognized clinical features of early myelofibrosis is an increased platelet count. Interleukin-11 is secreted from polarized cells or fibroblasts in response to injury. In polarized cells, interleukin-11 causes cellular dysfunction and can induce apoptosis, simultaneously suppressing cellular regeneration. In stromal cells, interleukin-11 triggers extracellular matrix production and invasion and migration of myofibroblasts. Interleukin-11-activated fibroblasts and myofibroblasts secrete cytokines and chemokines and are therefore strongly pro-inflammatory. Inhibition of interleukin-11 protects cytokinesis, is anti-fibrotic, and reduces stromal-induced inflammation. In tissues with regenerative capacity, inhibition of interleukin-11 allows proliferation and repopulation of damaged cells and organ regeneration. This family of cytokines and their cognate receptors are important contributors to cancer biology and may serve as potential biomarkers in disease progression, which has recently emerged as a biomarker promoting cancerous transformations[3-6].

in 1993, interleukin-17 was discovered in murine T-cell hybridoma clones and identified as cytotoxic T lymphocyte-associated antigen 8 (CTLA-8). It was also known as interleukin-17A. In mammals, there are currently six identified members of the interleukin 17 family: -17A, -17B, -17C, -17D, -17E, and -17F. Each family member shares some degree of amino acid sequence homology with interleukin-17A, ranging from less than 20% to 55%. The Interleukin-17 family of cytokines are homogeneous glycoproteins, or heterogeneous in the case of the cytokine IL-17A/F, and their molecular weights range between 35 and 50 kD. This family performs diverse functions, and this diversity is due in part to the complexity of the cellular functions stimulated by these cytokines. Interleukin-17 signaling functions determine biological action. The source of interleukin-17 production plays a major role in determining the immune response. It is worth noting that the interleukin 17 family plays a vital role in combating fungi, viruses, and extracellular bacteria, especially on skin and mucous surfaces. On the other hand, these proinflammatory molecules contribute effectively to the occurrence of a number of inflammatory diseases[7-9].

Materials and Methods

Patients and healthy controls:ninety participants were included in the current study, depending on their health status, participants were classified into 70 patients with type 2 diabetes and 20 healthy control groups.

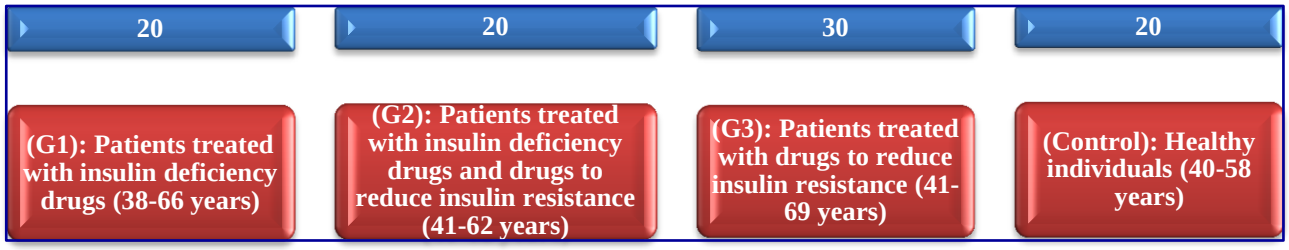

Figure 1:Distribution of the Study Individuals Basing on Their Health Status

Cases of patients with type 2 diabetes were collected from the Diabetes and Endocrinology Center in Al-Sadr Medical City-Al Najaf Governorate. Healthy samples were collected from the study population environment, such as housewives, postgraduate students, as well as workers in the hospital where infected samples were also collected.

Inclusion criteria of the patients and healthy controls:the current study included individuals diagnosed as patients with type 2 diabetes and treated either with drugs to compensate for the decrease in the level of insulin produced, or patients treated with drugs to modify the affinity of insulin receptors, the hormone, or both types of treatments, provided that the patient does not suffer from the development of diabetes or the emergence of complications resulting from it. Healthy individuals were selected as a control group based on several criteria that included: they do not suffer from any type of diabetes or metabolic disorders, that they are of a similar age to the individuals in the patient group, that they have a dietary pattern similar to the individuals in the disease group, and that they do not take any medication, finally, they look healthy.

Exclusion criteria of the study: the current study required exclusion the following cases: all patients who suffered complications resulting from the progression of type 2 diabetes, as well as participants (type 2 diabetic patients or healthy controls) who had suffered chronic diseases, *i.e.*; liver, renal, thyroid, cardiovascular diseases, hypertension, autoimmune diseases, and morbid obesity from participating in the current study. Cases who underwent surgery within 5 years, smokers and alcohol drinkers.

Samples collection: approximately at 9 AM in the morning, after at least 8 hours fasting, 5 milliliters of venous blood samples were collected from the type 2 diabetic patients and healthy individuals using gel tubes. After separating the serum from the study samples using a centrifuge at 5000 ×g for 5 minutes. Serum samples were preserved using Eppendorf tubes at -20°C after each sample was divided into 2 parts and stored until use.Colorimetric method was applied for measuring glucose, and

sandwich-ELISA method was applied to evaluate insulin, interleukin-11 and interleukin-17 in the study samples using human ELISA kitswhich furnished bySun Long Biotech Com., LTD, China. HOMA-IR was calculated mathematically for all subjects participating in the study, patients and healthy ones, according to the following equations:

$$\mathbf{HOMA-IR} = \frac{\mathbf{F.B.S(mg/dL)} \times \mathbf{Insulin\ (\mu U/mL)}}{\mathbf{405}}$$

Quantitative insulin sensitivity check index (QUICKI) formula was calculated mathematically for all subjects participating in the study, patients and healthy ones, according to the following equations:

$$\text{QUICKI} = \frac{\mathbf{1}}{\mathbf{log\ (fastinginsulin\mu U/mL)} + \mathbf{log\ (fastingglucosemg/dL)}}$$

Statistical analysis: the outcomes of the present study were analyzed through the statistical package for the social sciences (SPSS) version 26 software application statistical analysis system and excel (statistical package). The variables were illustrated by mean±S.D, minimum, maximum, frequencies, and percentages. Graphics are presented using pie and bar charts. Inferential data analysis includes: One way analysis of variance (ANOVA) test was applied for examining the probable variations among the evaluated biochemicals. Pearson's correlation was applied to determine the relation among the biochemical parameters of the present study. The probability of deflection than controls are considered statistically significant if *p*-value is below 0.05.

Results and Discussion

Spotlight on the demographic characteristics of the study participants:the present study included the participating of 90 individuals, who were divided into four groups, three of them (70 cases) were patients with previously documented type 2 diabetes mellitus (T2DM). The first illness group (G1) included 20 patients (10 males and 10 females) who were treated with insulin deficiency drugs only. The second group (G2) also included 20 patients (10 males and 10 females) who were treated with insulin deficiency drugs in addition to the drugs for reducing insulin resistance. While the third illness group (G3) included 30 patients (15 males and 15 females) who were treated with drugs to reduce insulin resistance. The last group included 20 healthy controls (10 males and 10 females).Demographic information indicates that all study patients underwent treatment to deal with the symptoms of type 2 diabetes, while members of the control group did not take any treatment during the period of obtaining the samples or before the start of the study, with emphasis on the fact that members of this group do not suffer from inflammatory diseases.The results in **Table 1** indicate that half of G1 members had a family history of diabetes in one or both parents, while the second group included 8 out of 20 patients with a family history,as

for the group subject to treatment with drugs that improve the binding of the insulin hormone to its receptors (G3) included 14 out of 30 patients with a family history of diabetes. The study was based on the fact that the control group members had no history of diabetes.The study indicated that the period of diagnosis of the infection that preceded the start of the study ranged between one year and 30 years in general, while the highest infection period was in the first pathological, while the shortest period was recorded G3. The statistical analysis indicated that there was a statistical difference in the period of diagnosis between G1 and G3 among patients, while the difference was not statistically acceptable comparing the period of infection in G1 and G2 or G2 and G3; respectively.Finally, it was noted that the majority of T2DM patients participating in the current work are city residents, and this is consistent with previous studies that indicate that the city lifestyle induces diabetes[10].

Table 1: Baseline Demographic Characteristics of The Participants in The Study

Parameters	*Type 2 Diabetic Patients*			*Controls (n=20)*
	G1 (n=20)	*G2 (n=20)*	*G3 (n=30)*	
Sex (Female / Male)	**10/10**	**10/10**	**15/15**	**10/10**
Treated/Untreated	**20/0**	**20/0**	**30/0**	**-**
Familiar History (Yes/No)	**10/10**	**8/12**	**14/16**	**-**
Duration of Disease (Year) (Mean± SD) Minimum-Maximum	**13.200±7.046 3-23**	**12.650±7.322 2-30**	**9.100±5.732 1-22**	**-**
Rural/Urban	**3/17**	**1/19**	**1/29**	**0/20**

Assessment of glucose levels in the samples of patients and healthy individuals: the results of the statistical analysis for fasting glucose analysis data showed that there were no significant differences ($p>0.05$) when comparing the groups with T2DM (G1, G2 and G3) with each other. In contrast, the study showed that there were significant differences ($p=0.000$) when comparing the three disease groups with the control group, as shown in **Table 2**.

Table 2: Glucose Levels in the Serum Samples of the Studied Groups

Subjects (n)	*Glucose (mg/dL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	**222.350±95.568**	**52.000-391.000**	**0.054 For G1*vs* G2** **0.401 For G1 *vs* G3** **0.000 For G1 *vs* C** **0.200 For G2 *vs* G3** **0.000 For G2 *vs* C** **0.000 For G3 *vs* C**
G2 Patients (20)	**178.750±80.752**	**95.000-344.000**	
G3 Patients (30)	**205.133±66.374**	**86.000-370.000**	
Controls (20)	**86.450±16.122**	**61.000-119.000**	

In order to evaluate the effect of sex on patients' response to medications used to treat diabetes, members of the study groups were divided into 8 subgroups (females and

males). The study showed that there were no significant differences when comparing between the sexes in one group (regardless of the health status of the group members).On the other hand, the study demonstrated the presence of statistical differences ($p<0.05$) when comparing the glucose levels of females in the T2DM groups with their counterparts in the control group. In the same manner, the results of comparing the glucose levels of males in the three diabetes groups with their peers in the control group were statistically clear (**Table 3**).

Table 3:Concentration of Glucose in the Samples ofthe Study Subgroups

Subjects (n)	*Sex (n)*	*Glucose(mg/dL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	**Female 10**	**205.600±96.435**	**52.000-391.000**	**0.292 For 1 *vs* 2**
	Male 10	**239.100±96.738**	**94.000-358.000**	**0.099 For 3 *vs* 4**
G2 Patients (20)	**Female 10**	**152.400±67.772**	**97.000-329.000**	**0.614 For 5 *vs* 6**
	Male 10	**205.100±87.351**	**95.000-344.000**	**0.892 For 7 *vs* 8**
G3 Patients (30)	**Female 15**	**198.600±74.534**	**119.000-370.000**	**0.096 For 1 *vs* 3**
	Male 15	**211.666±58.983**	**86.000-286.000**	**0.809 For 1 *vs* 5**
Controls (20)	**Female 10**	**84.300±17.789**	**61.000-108.000**	**0.000 For 1 *vs* 7**
	Male 10	**88.600±14.901**	**63.000-119.000**	**0.113 For 3 *vs* 5**
				0.034 For 3 *vs* 7
				0.000 For 5 *vs* 7
				0.285 For 2 *vs* 4
				0.344 For 2 *vs* 6
				0.000 For 2 *vs* 8
				0.820 For 4 *vs* 6
				0.000 For 4 *vs* 8
				0.000 For 6 *vs* 8

In general, medications used to treat hyperglycemia significantly lower blood glucose levels, but do not return to their levels in healthy individuals.The study showed a higher blood sugar level in diabetic patients (regardless of the type of treatment used) compared to healthy people. This increase can be explained by several reasons, including: failure of diabetics to adhere to the appropriate diet for them, with excessive consumption of carbohydrates in particular. The reason for the significant increase in blood glucose levels may be that patients may not be adhering to the appropriate dosage of the medications prescribed to them or the timing of taking them. One of the causes of high blood glucose may be due to activation of gluconeogenesis pathway (synthesis of glucose from non-carbohydrate sources) in response to hypoglycemia that resulting from receiving of patient a higher than permissible dose of diabetes medications.

Measurement of Insulin Concentrations in The Study Groups: Insulin levels were evaluated in the samples of the four study groups, and then the results were statistically analyzed using ANOVA test.The results of the current study indicate to the absence of significant differences in implicit comparisons of the diabetic groups

(G1, G2 and G3) or when compared them with the control group, as illustrated in **Table 4**.

Table 4: Levels of Insulin in the Different Diabetic Patients and Healthy Groups

Subjects (n)	*Insulin (mIU/L) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	11.379±8.759	0.966-29.410	0.754 For G1 *vs* G2 0.784 For G1 *vs* G3 0.858 For G1 *vs* C 0.944 For G2 *vs* G3 0.893 For G2 *vs* C 0.938 For G3 *vs* C
G2 Patients (20)	10.504±9.368	1.380-27.248	
G3 Patients (30)	10.682±7.751	0.775-27.091	
Controls (20)	10.880±9.638	0.836-29.811	

The comparison was made among subgroups of the study using the ANOVA test, which showed that there were no significant differences ($p>0.05$) when comparing insulin levels between the sexes for the same group, as well as when comparing members of the same sex in the different groups, whether they were females or males, as shown in **Table 5.**

Table 5: Levels of Insulin in the Type 2 Diabetic Patients and Healthy Subgroups

Subjects (n)	*Sex (n)*	*Insulin(mg/dL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	Female 10	12.603±9.282	1.108-29.410	0.542 For 1 *vs* 2 0.767 For 3 *vs* 4 0.425 For 5 *vs* 6 0.966 For 7 *vs* 8 0.502 For 1 *vs* 3 0.378 For 1 *vs* 5 0.683 For 1 *vs* 7 0.883 For 3 *vs*5 0.793 For 3 *vs*7 0.664 For 5 *vs*7 0.814 For 2 *vs*4 0.616 For 2 *vs* 6 0.873 For 2 *vs* 8 0.807 For 4 *vs* 6 0.940 For 4 *vs* 8 0.744 For 6 *vs* 8
	Male 10	10.155±8.512	0.966-24.460	
G2 Patients (20)	Female 10	9.912±9.671	1.380-24.208	
	Male 10	11.097±9.538	1.455-27.248	
G3 Patients (30)	Female 15	9.374±7.910	0.775-27.091	
	Male 15	11.990±7.629	1.877-24.398	
Controls (20)	Female 10	10.965±10.704	1.020-29.811	
	Male 10	10.795±9.029	0.836-27.764	

Evaluation of homeostatic model assessment insulin resistance and quantitative insulin sensitivity check index in the study groups: both HOMA-IR and QUICKI were calculated for the study samples. The results in **Tables 6** and **7** indicate that

there are no significant differences (p>0.05) when comparing the proportions of HOMA-IR and QUICKI in groups of patients with type 2 diabetes in the three groups with each other.On the other hand, the study indicated that there were significant differences when comparing the HOMA-IR ratios of the three disease groups with the control group, while the statistical differences in the QUICKI ratios were limited for comparing the control group to both G1 (p=0.039) and G2 (p=0.015), respectively.

Table 6: Ratios of Homeostatic Model Assessment Insulin Resistance in the Study Groups

Subjects (n)	*HOMA-IR Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	6.258±5.560	0.140-18.180	0.516 For G1 *vs* G2 0.583 For G1 *vs* G3 0.008 For G1 *vs* C 0.871 For G2 *vs* G3 0.042 For G2 *vs* C 0.017 For G3 *vs* C
G2 Patients (20)	5.290±6.094	0.340-21.330	
G3 Patients (30)	5.510±4.300	0.280-15.240	
Controls (20)	2.220±1.830	0.160-6.070	

Table 7: Ratios of Quantitative Insulin Sensitivity Check Index in the Study Groups

Subjects (n)	*QUICKI Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	0.330±0.078	0.260-0.570	0.610 For G1 *vs* G2 0.852 For G1 *vs* G3 0.039 For G1 *vs* C 0.457 For G2 *vs* G3 0.117 For G2 *vs* C 0.015 For G3 *vs* C
G2 Patients (20)	0.341±0.064	0.250-0.470	
G3 Patients (30)	0.326±0.058	0.260-0.490	
Controls (20)	0.375±0.074	0.290-0.550	

The study revealed that there were statistically significant differences when comparing HOMA-IR ratio of the females in G1 with their peers in the control group (p=0.047), as well as when comparing the males of the second (p=0.046) and third groups (p=0.018) with their counterparts of the same sex in the control group (**Table 8)**.The study did not record any differences in QUICKI ratios among participants in the current work of the same sex, except when comparing the QUICKI ratios of the males of the third group with their healthy peers (**Table 9)**.

Table 8: Ratios of Homeostatic Model Assessment Insulin Resistance in the Study Subgroups

Subjects (n)	*Sex (n)*	*HOMA-IR Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	Female 10	6.352±5.395	0.140-17.570	0.929 For 1 *vs* 2 0.233 For 3 *vs* 4 0.098 For 5 *vs* 6
	Male	6.164±6.012	0.270-18.180	

	10			0.931 For 7 *vs* 8
G2 Patients (20)	Female 10	4.032±5.319	0.480-17.370	0.271 For 1 *vs* 3 0.238 For 1 *vs* 5
	Male 10	6.549±6.825	0.340-21.330	0.047 For 1 *vs* 7 0.981 For 3 *vs* 5
G3 Patients (30)	Female 15	4.078±2.979	0.280-9.950	0.367 For 3 *vs* 7 0.311 For 5 *vs* 7
	Male 15	6.942±5.004	0.430-15.240	0.855 For 2 *vs* 4 0.685 For 2 *vs* 6
Controls (20)	Female 10	2.130±1.856	0.270-4.800	0.070 For 2 *vs* 8 0.837 For 4 *vs* 6
	Male 10	2.311±1.900	0.160-6.070	0.046 For 4 *vs* 8 0.018 For 6 *vs* 8

Table 9:Ratios of Quantitative Insulin Sensitivity Check Index in the Study Subgroups

Subjects (n)	*Sex (n)*	*QUICKI Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	Female 10	0.330±0.091	0.260-0.570	1.000 For 1 *vs* 2 0.402 For 3 *vs* 4
	Male 10	0.330±0.067	0.260-0.490	0.477 For 5 *vs* 6 0.897 For 7 *vs* 8
G2 Patients (20)	Female 10	0.354±0.061	0.260-0.440	0.439 For 1 *vs* 3 0.850 For 1 *vs* 5
	Male 10	0.328±0.068	0.250-0.470	0.132 For 1 *vs* 7 0.510 For 3 *vs* 5
G3 Patients (30)	Female 15	0.335±0.057	0.280-0.490	0.459 For 3 *vs* 7 0.143 For 5 *vs* 7
	Male 15	0.317±0.059	0.260-0.450	0.949 For 2 *vs* 4 0.654 For 2 *vs* 6
Controls (20)	Female 10	0.377±0.069	0.300-0.490	0.168 For 2 *vs* 8 0.706 For 4 *vs* 6
	Male 10	0.373±0.081	0.290-0.550	0.149 For 4 *vs* 8 0.050 For 6 *vs* 8

Levels of interleukin-11 in the patients and control groups: The levels of interleukin-11 were evaluated in the samples of the four study groups, and the statistical analysis of the results of the current work showed the absence of significant differences when comparing the groups with diabetes with each other or with the control group, except the observed result of a significant decrease in the concentration of interleukin-11 in the third group compared to the control group, as shown in **Table 10**.

Table 10: Levels of Interleukin-11 in the Diabetic and Control Individuals

Subjects (n)	*Interleukin-11 (pg/mL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	11.120±6.062	3.690-23.108	0.999 For G1 *vs*G2 0.594 For G1 *vs*G3 0.315 For G1 *vs*C 0.595 For G2*vs*G3 0.315 For G2*vs*C 0.050 For G3 *vs* C
G2 Patients (20)	11.115±9.452	2.318-39.330	
G3 Patients (30)	9.788±5.989	3.218-26.708	
Controls (20)	13.871±12.453	2.993-49.253	

In **Table 11**, the results of the study indicate that there is no statistical significance when comparing between the sexes in one group (whether it is one of the diabetic groups or the healthy group) when comparing the levels of interleukin-11 between the sexes. This is also the case when comparing females with each other in groups with T2DM, except for the significant difference observed when comparing the levels of interleukin-11 for G1 females with their counterparts in G3,in the same way; a statistical difference was observed when comparing the levels of this protein in the samples of G3 females with their counterparts in the control group. While the study did not record any statistically significant differences between the males in the four groups (sick and healthy). It was found that the lowest rate of interleukin-11 was for G3 females among the female groups participating in the study. This indicates a link between the change in interleukin-11 levels in groups of women with diabetes in general and those suffering from insulin resistance in particular.

Table 11: Levels of Interleukin-11 (pg/mL) in the Subgroups of Diabetic and Controls

Subjects (n)	*Sex (n)*	*Interleukin-11 (pg/mL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	Female 10	14.789±6.108	6.120-23.108	0.054 For 1 *vs* 2 0.431 For 3 *vs* 4 0.233 For 5 *vs* 6 0.101 For 7 *vs* 8 0.173 For 1 *vs* 3 0.049 For 1 *vs* 5 0.561 For 1 *vs* 7 0.625 For 3 *vs* 5 0.054 For 3 *vs* 7 0.010 For 5 *vs* 7 0.174 For 2 *vs* 4 0.226 For 2 *vs* 6 0.380 For 2 *vs* 8 0.777 For 4 *vs* 6 0.626For 4 *vs* 8 0.801For 6 *vs* 8
	Male 10	7.449±3.218	3.690-12.600	
G2 Patients (20)	Female 10	9.630±5.919	2.318-21.330	
	Male 10	12.600±12.193	2.880-39.330	
G3 Patients (30)	Female 15	7.948±3.300	3.218-14.108	
	Male 15	11.628±7.493	4.545-26.708	
Controls (20)	Female 10	16.980±15.357	4.073-49.253	
	Male 10	10.761±8.370	2.993-30.488	

Concentrations ofinterleukin-17 in the study groups: The levels of interleukin-17 were assessed in the samples of the study groups, the results showed that there was no statistical significance when comparing the levels of interleukin-17 in the three disease groups with each other, as well as, when comparing them with the healthy group. Although the present study illustrated elevated interleukin-17 level (65.519 pg/mL) in the sample of 52 years old diabetic female patient in G2, but the study showed that levels of interleukin-17of the diabetic patients were closed to what was noted in the control group, and this indicates that interleukin-17 is a good parameter for evaluating the T2DM patients respond to treatment in the three disease groups, regardless of the type of treatment used, as **Table 12** illustrates.

Table 12:LevelsInterleukin-17 (pg/mL) in the Groups of Diabetic and Controls

Subjects (n)	*Interleukin-17(pg/mL) Mean ± SD*	*Minimum-Maximum*	*p-value*
G1 Patients (20)	**39.280±8.818**	**30.048-59.030**	**0.056For G1 *vs* G2 0.180For G1 *vs* G3 0.090For G1 *vs* C 0.444For G2 *vs* G3 0.824For G2 *vs* C 0.600For G3 *vs* C**
G2 Patients (20)	**34.524±8.906**	**25.337-65.519**	
G3 Patients (30)	**36.250±7.429**	**26.759-51.651**	
Controls (20)	**35.071±5.633**	**26.581-44.183**	

Results of the present study showed that there were statistically significant differences between males and females of G1 only among the groups participating in the current work, as the levels of interleukin-17 witnessed an increase in interleukin-17 concentrations of female samples compared to males. The results also showed that there were clear significant differences between females of G1 and their counterparts in G2 (p=0.043) and G3 (p=0.002), as well as females of the healthy group (p=0.001). Moreover, it has been observed that the high levels of interleukin-17 in diabetic female patients caused by reduction in the insulin production, which means that interleukin-17 elevation is associated with a defect in β-cells, exclusively in women. While, the study showed that there were no statistically significant variations in theinterleukin-17 when the comparison was done among male subgroups together, except for one significant difference when comparing the males of G2 and G3 together (p=0.032) only, where the increase in the level of interleukin-17 in favor of the G3 males (**Table 13**).

Table 13: Levels Interleukin-17 (pg/mL) in the Diabetic and Healthy Persons

Subjects (n)	*Sex (n)*	*Interleukin-17 (pg/mL) Mean ± SD*	*Minimum-Maximum*	*p-value*

G1 Patients (20)	Female 10	44.192±9.869	30.493-59.030	0.004 For 1 *vs* 2
	Male 10	34.368±3.627	30.048-41.427	0.076 For 3 *vs* 4
G2 Patients (20)	Female 10	37.462±11.184	27.292-65.519	0.174 For 5 *vs* 6
	Male 10	31.586±4.816	25.337-40.805	0.312 For 7 *vs* 8
G3 Patients (30)	Female 15	34.422±7.415	26.759-51.651	0.043 For 1 *vs* 3
	Male 15	38.078±7.223	26.848-51.651	0.002 For 1 *vs* 5
Controls (20)	Female 10	33.408±4.550	28.270-42.761	0.001 For 1 *vs* 7
	Male 10	36.733±6.335	26.581-44.183	0.311 For 3 *vs* 5
				0.218 For 3 *vs* 7
				0.735 For 5 *vs* 7
				0.397 For 2 *vs* 4
				0.217 For 2 *vs* 6
				0.471 For 2 *vs* 8
				0.032 For 4 *vs* 6
				0.119 For 4 *vs* 8
				0.653 For 6 *vs* 8

Mainly, interleukin-17 is one of the predominant inflammatory factors that can over-express pro-inflammatory genes via triggering NF-κB, MAPK, and C/EBP cascades, whether alone or in combination with other cytokines. These mediators prevent glucose absorption by suppressing insulin signaling via the receptor. Worsening of obesity increases the secretion of inflammatory factors from the liver, islets of the pancreas, and visceral adipose tissue, creating a hyper-inflammatory condition that deteriorates IR and leads to poor glucose control. Recently, the adaptive immune system has also been studied in the pathogenesis of T2DM. T-helper-17 cell (TH17) is one of the distinct CD4+ helper T cell subsets contributing to T2DM immune pathogenesis by interleukin-17 secretion[11]. Interleukin-17, as a pro-inflammatory

cytokine, contributes to the development of diabetes, and its levels have been studied in many previous studies that focused specifically on evaluating its levels in patients newly diagnosed with the disease (before receiving treatment) or those suffering from the emergence of severe complications chronic type 2 diabetes[12].The current study was designed to study the damage caused by T2DM treated with different drugs according to the type of defect that caused the rise in blood sugar levels, provided that the disease has not progressed to the stage of complications resulting from diabetes. The levels of interleukin-17 evaluated in the study groups indicated infected and healthy individuals depend on the body's response to treatments used to prevent the occurrence of acute or chronic complications, as the study demonstrated that the levels of this parameter in the three infected groups (G1, G2, and G3) were close to those found in members of the healthy group. The results of the present study were consistent with the findings of Roohi, *et al.*, and Vasanthakumar, *et al.*, in their studies, which showed no significant difference in the level of interleukin-17 between T2DM and controls [13,14].While the results of the current work are contrary to Parhi, *et al.*, study which showed an increase in the level of interleukin-17 in samples of newly diagnosed T2DM patients compared to healthy controls. The Interleukin-17 level was higher in the group of patients with severe complications[7,15]. Also in the study of Barhi, *et al.*, the level of interleukin-17 was highest in the group with chronic complications[7], and this finding is supported by Yousefidaredor, *et al.*, who found that interleukin 17 plays an important role in the development of T2DM and its complications through up-regulation of T2DM several inflammatory molecules including angiotensin II type I receptor and molecules associated with the JAK2 STAT3 pathway, these findings suggest that Interleukin-17 is a contributing factor to the inflammatory process in T2DM and its complications[16]**.**

Relationships of interleukin-11 to the age, body mass index and the variables connecting to the glucose levels in the diabetic patients and healthy individuals:the current study indicated that there were excellent positive correlations between interleukin-11 and insulin in G1 (r=0.451 at p=0.046), G2 (r=0.517 at p=0.020), and the healthy group (r=0.674 at p=0.001). With the same manner, there was a high positive correlation between interleukin-11 and HOMA-IR in both G2 (r=0.595 at p=0.006) and control individuals (r=0.645 at p=0.002).On the contrary, there was a negative correlation between interleukin-11 and QUICKI (r=-0.541 at p=0.014) in the control group only. While the study did not show acceptable relationships for this criterion (interleukin-11) with each of age, BMI and glucose in the studied groups, as demonstrates in **Table 14**.

Table 14: Relationship of Interleukin-11 to the Other Criteria of the Diabetic and Controls

Parameters	*Subjects*							
	G1		*G2*		*G3*		*Controls*	
	r	*p*	*r*	*p*	*r*	*p*	*R*	*p*

Age	**-0.210**	**0.374**	**0.223**	**0.344**	**0.040**	**0.836**	**-0.040**	**0.866**
BMI	**0.214**	**0.366**	**-0.225**	**0.340**	**0.087**	**0.646**	**-0.155**	**0.514**
Glucose	**-0.126**	**0.598**	**0.347**	**0.134**	**0.187**	**0.322**	**-0.154**	**0.518**
Insulin	**0.451***	**0.046**	**0.517***	**0.020**	**0.167**	**0.377**	**0.674****	**0.001**
HOMA-IR	**0.210**	**0.375**	**0.595****	**0.006**	**0.194**	**0.304**	**0.645****	**0.002**
QUICKI	**-0.370**	**0.109**	**-0.382**	**0.097**	**-0.283**	**0.129**	**-0.541***	**0.014**

Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level.

Relationships of interleukin-17 to the age, body mass index and the variables connecting to the glucose levels in the diabetic patients and healthy individuals: the statistical analysis of the correlation between interleukin-17 and each of the age, BMI, glucose, insulin, HOMA-IR, and QUICKI indicates that there is a positive relationship between interleukin-17 and insulin (r=0.490 at p=0.028) in members of G1, as well as a negative relationship was observed between interleukin-17 and QUICKI (r=-0.379 at p=0.039) in the group of diabetic patients with insulin resistance (G3). While the correlations were devoid of statistical acceptability when comparing this parameter (interleukin-17) with the other criteria that were evaluated in the four groups, as shown in **Table 15.**

Table 15: Relationship of Interleukin-17 to the Other Criteria of the Diabetic and Controls

Parameters	***Subjects***							
	G1		***G2***		***G3***		***Controls***	
	r	***p***	***r***	***p***	***r***	***p***	***R***	***p***
Age	**-0.035**	**0.883**	**0.138**	**0.563**	**0.012**	**0.948**	**-0.129**	**0.587**
BMI	**0.072**	**0.762**	**-0.023**	**0.922**	**-0.027**	**0.888**	**0.065**	**0.784**
Glucose	**-0.204**	**0.389**	**-0.184**	**0.438**	**-0.112**	**0.555**	**-0.313**	**0.179**
Insulin	**0.490***	**0.028**	**0.049**	**0.839**	**0.341**	**0.066**	**0.171**	**0.470**
HOMA-IR	**0.358**	**0.121**	**-0.099**	**0.678**	**0.318**	**0.087**	**0.141**	**0.554**
QUICKI	**-0.245**	**0.298**	**-0.094**	**0.694**	**-0.379***	**0.039**	**-0.004**	**0.988**

Correlation is significant at the 0.05 level

Relationship between interleukin-11 and interleukin-17 in the Type 2 Diabetics and controls: When evaluating potential relationships between the two criteria evaluated in current work in people with type 2 diabetes and controls, **Table 16** shows a significant positive correlation between interleukin-17 and interleukin-11 (~70%, at p=0.033) in a group of type 2 diabetic patients who treated with drugs supplemented to suppress insulin production only.

Table 16: Relationship of Interleukin-11 to Interleukin-17 of the Diabetics and Controls

Interleukin-11 and Interleukin-17	*Subjects*							
	G1		*G2*		*G3*		*Controls*	
	r	***p***	***r***	***p***	***r***	***p***	***R***	***p***
	0.695*	**0.033**	**0.047**	**0.843**	**0.093**	**0.624**	**-0.179**	**0.450**

Correlation is significant at the 0.05 level

Conclusion

Type 2 diabetes is not linked to one sex or another or one age, but the most common age group for symptoms of the disease to appear are individuals in the fifth and sixth decades. Receiving diabetes treatments in general does not return blood sugar levels to normal limits. During insulin resistance progresses, there will be a decline in the production of anti-inflammatory proteins, including interleukin-11. Interleukin-17 is a good parameter for evaluating the T2DM patients respond to treatment in the three disease groups, regardless of the type of treatment used.

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