Original Article

Correlation between Serum Interleukin-12 and Lipid Profiles in Non-Insulin-Dependent Diabetic Patients

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Abstract

The current study aimed to evaluate the level of IL12 CYTOKINE and how it correlates with the level of lipids in diabetic patients. The results indicated a mean elevation in IL-12 levels among the research participants (11.85: SE 0.64) compared to the control group (6.63: SE 0.34). This cytokine may be critical in the development of T2DM, in which inflammatory reactions associated with IL-12 gene expression are accelerated by interfering with excessive insulin concentration. It also showed an insignificant correlation between this cytokine and lipid levels

INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic disorders known by hyperglycemia caused by fault in insulin secretion or action or both (Safar et al., 2013). Diabetes mellitus caused many complications such as macrovascular and microvascular (Albrechtsen et al., 2013). International Diabetes Federation (IDF) (2013) has shown that 371 million people whom suffer from diabetes worldwide, and it may increase up to 552 million by 2030, meaning that, there are three new cases every second (Almdal et al., 2008; Al-Safar et al., 2014). Diabetes mellitus had been classified into three major types: Type 1 diabetes mellitus (T1DM) which is characterized by beta cell destruction, usually leading to absolute insulin deficiency , type 2 diabetes mellitus (T2DM), which is the most predominant type and is characterized by (insulin resistance) and gestational diabetes mellitus (GDM). Type 2 diabetes is an international health problem featured by a defect in insulin secretion and or a decrease in sensitivity to insulin, also termed insulin resistance (Al-Sinani et al., 2015).

Antigen-presenting cells including Dendritic Cells (DC), macrophages, and NK cells all release important cytokine (interleukin-12). It is crucial to the function of cell-mediated immunity. It influences several stages of the immune response, including NK cell maturation, the production of pro-inflammatory cytokines by NK cells and T cells like IFN-, IL-2, IL-3, and TNF-, and the activation of CD4+CD25- T cells in the presence of regulatory T cells along with other pro-inflammatory factors (Razooqi et al., 2022).

The members of the IL-12 family are heterodimeric proteins consisting of an alpha chain and a beta chain. The alpha chains consist of p19, p28, or p35 that share structural homology with IL-6, whereas the beta chains, p40 or Epstein-Barr virus-induced gene 3 (EBI3), shares homology with soluble cytokine receptor chains, such as IL-6 Rα (Goriely et al., 2008). Dimerization of specific alpha chain and beta chain subunits form the four known family members including IL-12 (i.e., p35 and p40), IL-23 (i.e., p19 and p40), IL-27 (i.e., p28 and EBI3), and the newly identified IL-35 (i.e., p35 and EBI3). Each cytokine signals through unique heterodimeric receptors that are composed of combinations of IL-12 Rβ1, IL-12 Rβ2, IL-23R, gp 130, and WSX-1 subunits (Collison et al., 2008).

IL-12 likely hastens the onset of macrovascular problems in T2DM and contributes to the creation of atherosclerotic plaque (Beadling et al., 2006). Furthermore, it has been discovered that increased glucose levels in diabetic mice trigger inflammatory responses linked to the production of the IL-12 cytokine gene (Wegner et al., 2008). However, it is unknown if elements connected to the development of T2DM, such as metabolic compensation, dysfunctional beta cell secretion, and insulin resistance, have an impact on IL-12 concentrations (International Diabetes Federation, 2021).

Materials and Methods

Subjects: The study was involved (150) subjects including (50) person apparently healthy individuals as a control group through using inclusion criteria which included as Fasting plasma glucose <100 mg/dl; No any past medical history for type 2 diabetes No family history of diabetes in first-degree relations no taking insulin or have T1DM and pregnancy. The entire sample was obtained from specialized clinics in the city of Kut during the period from February 2021 to February 2021. The patients were distributed between (35 males and 35 females), aged between 35-66 years.

Blood sampling: Five milliliters of venous blood were drawn by disposable syringe. Each blood sample was divided into 3 ml placed in a sterile plane tube and allowed to clot, and then serum was separated by centrifugation at 4000 rpm for 15 minutes. Serum was stored at -20ºC. These sera were used for estimating lipid profile. The remaining 2 ml of blood were put directly in EDTA tube for estimating HbA1c and DNA extraction.

Biochemical analysis: lipid profile and HbA1c were measured by COBAS automated analyzer Integra 400 Plus (Roch, Germaney).

Statistical analysis

Our data were analyzed using of ANOVA test in GraphPad Prism (6.0.1) Software at a significant differences of P□0.05 (Gharban and Yousif, 2020; 2021).

Results and discussion

Diabetic dyslipidemia is characterized by a change in the blood serum lipid concentration, including an increase in total cholesterol, LDL, TG, and low HDL (Santoes et al., 2014; Moraadian, 2009). The National Cholesterol Education Program (NCEP) Guideline states that hypercholesterolemia is defined as TC > 200 mg/dL, raised LDL-C when the value is > 100 mg/dL, elevated blood triglycerides as TAG > 150 mg/dL, and a reduction in HDL-C when the value is 40 mg/dL. A total 100 diabetes patients in all took part in this study. About 79 patients (32 males vs. 47 females), 65% (30 vs. 35) of patients, respectively, had elevated serum TG and LDL levels, whereas the level of good cholesterol is lower than the reference level in 78% (34% males vs. 44% females) of diabetic individuals. About 55 patients (55%) had high total cholesterol of over 200 mg/dl. As seen in figure, there was a distinct rise in lipid levels in diabetic females compared to males (Figure 1, Table 1).

This result is consistent with those of the forerunners (Vera et al., 2020). According to, the causes of this hyperlipidemia in females have been related to sex hormones' influence on body fat distribution, which result in variations in altered lipoproteins (Shahwan et al., 2019). The comparison of the mean value with the control group in our study revealed a significantly significant difference (P 0.01).

Similar findings have been reported in the past. According to Dinesh Kumar et al. (1967), older, untreated diabetics have higher blood cholesterol levels (238.50 mg/dl). They all made consistent notes, including Maleva (1961), Sharma et al. (1970), and Sosenko et al. (1980). In addition, obese individuals and men with diabetes who had stable blood sugar levels had higher serum cholesterol levels, according to Nikkila et al. (1978).

Blood sugar levels are high due to inadequate or lax regulation, or perhaps unintentionally as a result of obesity, the creation of cholesterol increases. A high concentration of plasma CHO, TG, and a reduction in plasma HDL levels cause insulin resistance with or without DM, which is closely associated to a qualitative shift in the lipid profile pattern. Any malfunction in carbohydrate metabolism results in a disorder in lipid metabolism (Del et al., 2013). With a mean level of 247.35 m 12.785 g/dl, triglyceride levels ranged from 83 mg/dl to 727 mg/dl and were statistically significant. Compared to diabetics with good control, those with poor control had higher levels of triglycerides (247.3 12.785). This is consistent with research by Piia P et al. (2012) and Akeel bai-Yaqobi et al. (2011) that demonstrated increased levels of triglyceride in diabetics.

Diabetes patients had very low levels of blood HDL cholesterol, which ranged from 26 mg/dl to 50 mg/dl on average. Numerous investigations have shown that there is no link between HbAC and serum cholesterol and triglyceride levels, as reported by Lopes-Virella et al. (1982). Falko et al. (1981) and Dave et al. (2019) found a similar strong inverse association between HbA1

C levels and HDL cholesterol levels in their studies (r= - 0.48, p=0.0001). HbA C levels and cholesterol and triglyceride levels also had a direct, statistically significant relationship. This is at odds with Peterson and colleagues' findings and concurs with Gonen et al. (1977).

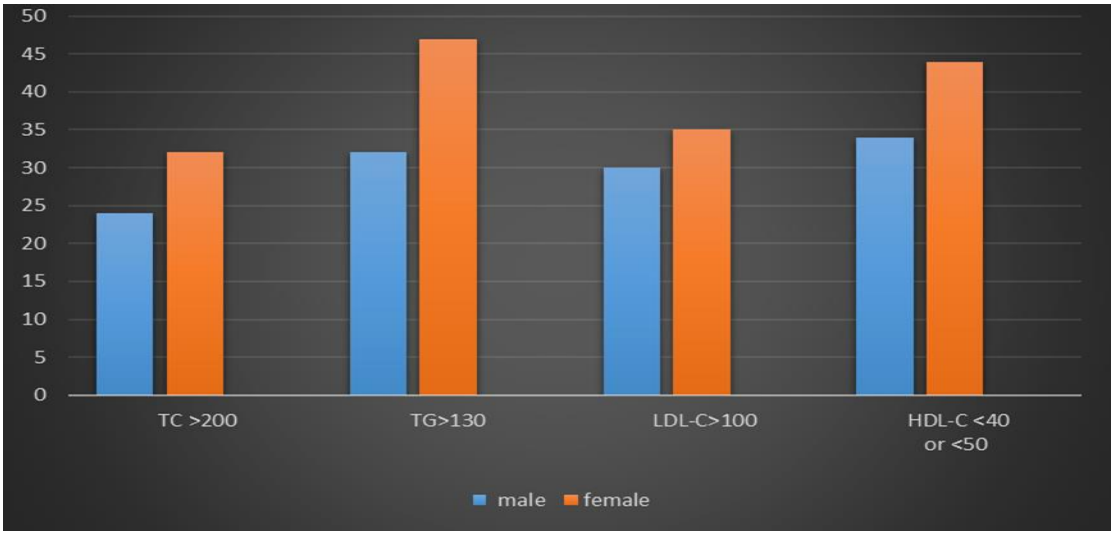


Figure (1): Results of lipid profile according to gender

Table (1): Values of lipid profile among the different study group

Group	Mean ± SE (mg/ml)				
	T. Cholesterol	Triglyceride	HDL	LDL	VLDL
Patients	203.69 ±5.22	247.35 ±12.785	36.69 ±0.45	118.73 ±4.59	49.52 ±2.55
Control	173.30 ±5.18	173.40 ±12.14	42.12 ±2.50	97.12 ±5.29	34.76 ±2.42
T-test	16.318	39.507	3.715	14.834	7.898
P-value	0.0003	0.0003	0.0045	0.0046	0.0003
(P≤0.01)					

Measuring serum IL-12 levels: Average IL-12 levels among participants in the research. The results explained the considerably higher mean blood IL-12 levels in diabetes individuals (11.85: SE 0.64) compared to the control group (6.63: SE 0.34), (Table 2). This cytokine may be crucial in the development of T2DM, According to Wen et al. (2006), inflammatory interactions associated with IL-12 gene expression are accelerated by hyperglycemia in diabetic rats or by interfering with the excessive concentration of insulin (Hauer et al., 2005).

Table (2): Results of IL-17 among

Parameter / Groups	**Control N=50**	**Patients N=100**	**P-values**	**T-test**
IL-17 pg/ml (mean± SE)	6.63 ±0.34	11.85 ±0.64	0.0001	1.452 **

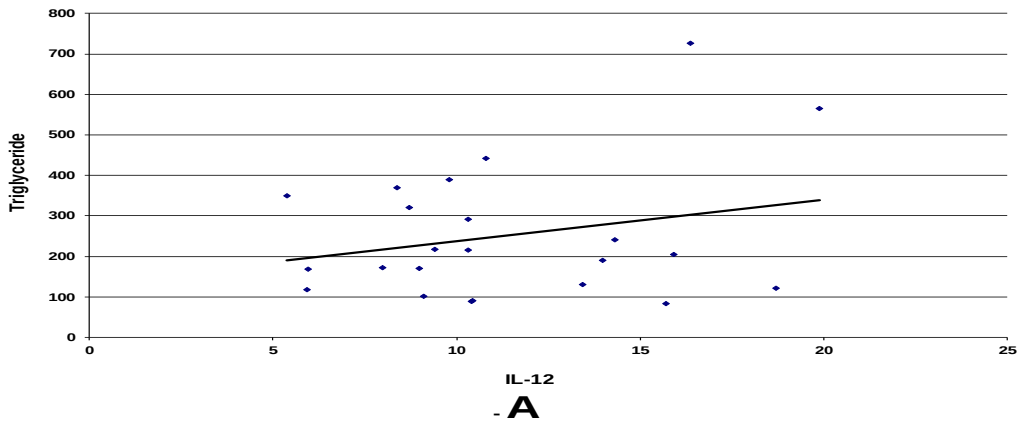
Furthermore, Tumor necrosis factor alpha (TNF-), IL-1 beta, and IL-12, which are released by monocytes and macrophages, may have a primary role in the damage to islet beta-cells, according to Blazher et al. (2006). In addition, elevated levels of IL12 have been seen in both kinds of diabetes (T1DM: XSE, pg/ml = 2.40.16, T2DM: 2.350.10) in comparison to healthy participants (1.860.07).

The influence of IL-12 changes in the blood of T2DM patients is yet unknown, however Sarsvik et al. proposed that IL-12 may play a role in the development of type 1 diabetes by inducing autoreactive T cell responses, which may lead to self-destructive immunity in the absence of infection. It influences a number of immune response stages, including NK cell maturation, CD4-CD25 T cell activation, and the production of pro-inflammatory cytokines by T cells and NK cells such as Interferon-(IFN-), IL-2, IL-3, and TNF-.

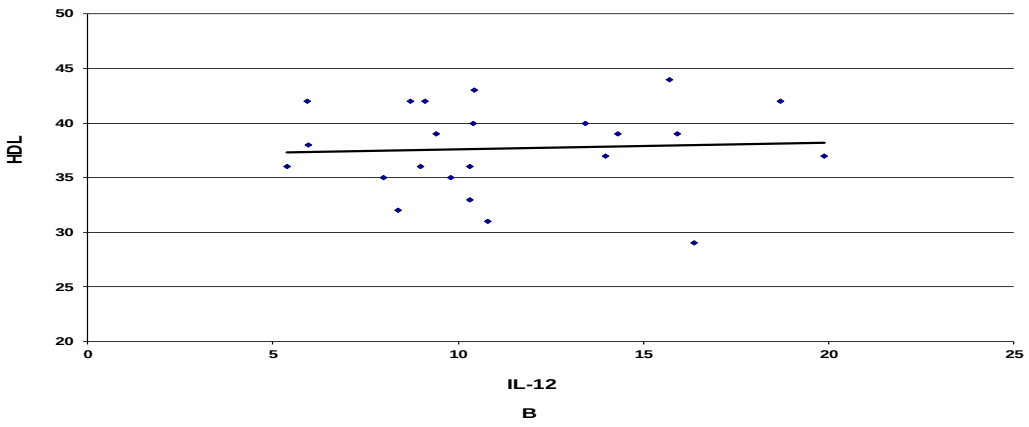
IL-12 controls naïve T cells as well. Interleukin-12 concentrations are regulated by parameters like insulin resistance and beta-cell dysfunction, according to a number of recent studies, although Wegner and colleagues (2008) find that its level in diabetic patients is only correlated with the pro-insulin concentration (Wegner et al., 2008). By interfering with the high concentration of insulin and so speeding macrovascular problems, IL-12 plays a significant role in the pathogenesis of t2dm (Hauer and others, 2005).

Because the immune system's response to infections depends on IL-12, the effects of IL-12 variations in the blood of T2DM patients are yet unknown, despite evidence that IL-12-induced autoreactive T cell responses may predispose to self-destructive immunity in the absence of infection. While it is unknown whether factors associated with the progression of T2DM, such as metabolic compensation, beta cell secretory dysfunction, and insulin resistance, IL-12 concentrations were found to be primarily influenced by fasting pro-insulin concentration in a recent study (Wegner et al., 2008).

Besides that, it has been noted that the complicated interactions between insulin resistance, hsCRP, LDL and HDL-c from visceral fat and the adipose tissue, which is known for producing a variety of pro-inflammatory cytokines, are responsible for the increase in IL-12 levels in diabetes (Figure 2).



- A



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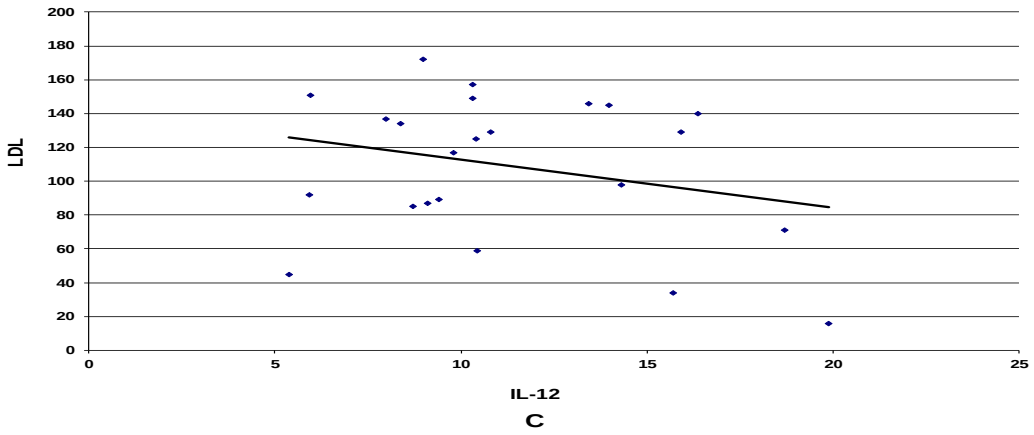

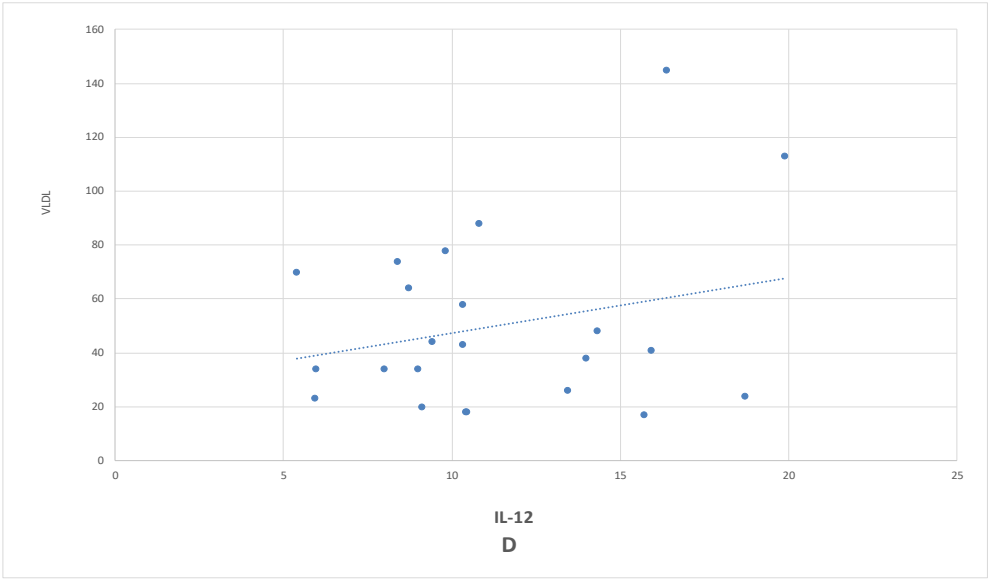

Figure (2): Relationship between IL-12 and TG, HDL, LDL and VLDL levels.

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