The Egyptian Journal of Hospital Medicine (October 2021) Vol. 85 (2), Page 4348-4352

Assessment of Interleukin 1-β in Controlled and Uncontrolled Type 2 Diabetic Patients

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ABSTRACT

Background: Type 2 diabetes has been identified as an immune-mediated disease characterised by poor insulin signaling and selective death of insulin-producing cells, with cytokines playing a key role. Disturbance of the anti-inflammatory response could be a key component of the type 2 diabetes-causing chronic inflammation. The cytokine family interleukin 1 (IL-1) plays a key function in endocrinology and the regulation of inflammatory stress responses.

Objective: The aim of this work is to assess the role of interleukin 1β, in patients with type 2 diabetes mellitus (controlled and uncontrolled) compared to healthy individuals.

Patients and Methods: A case control study was conducted on 80 adults, ranging from 25-60 year old, attending the endocrine or internal medicine clinic in Ain Shams University Hospital. They were divided into 3 groups :Group (1): 30 controlled type 2 diabetic patients on oral hypoglycemic. Group (2): 30 recently uncontrolled type 2 diabetic patients over the last 6 months, on oral hypoglycemic. Group (3): 20 healthy individuals.

Results: Serum IL-1β was significantly increased in recently uncontrolled diabetics than controlled diabetics and normal subjects. Serum IL-1β was positively correlated with fasting blood sugar (FBS), 2 hours post prandial (2 hrs PP), glycosylated Hemoglobin (HBA1C), triglycerides (TG) and HOMA IR and there was a negative correlation with high density lipoproteins (HDL).

Conclusion: The significant difference in the level of interleukin 1β among the studied groups highlights an implication of interleukin 1β in the pathogenesis of type 2 diabetic patients.

Keywords: Cytokines, Diabetes mellitus, Inteleukin1 β.

INTRODUCTION

Cytokines are a broad and diversified family of tiny cell signaling protein molecules. Interleukins and interferons, for example, are immunomodulating agents. Interleukin 1 (IL-1), Interleukin 6 (IL-6) and Tumor Necrosis Factor (TNF- α) are produced by virtually all nucleated cells, particularly endothelial, epithelial, and macrophage cells [(1)].

The interleukin 1 (IL-1) family plays a critical role in immunological and inflammatory response control. It controls the fundamental metabolic rate, blood glucose levels, and blood pressure, among other things. It also reduces insulin release and causes apoptosis in cells, resulting in type 2 diabetes. Polymorphisms in the interleukin 1 (IL-1) gene are type 2 diabetes susceptibility indicators in several populations [(2)].

Interleukin 1 (IL-1) is a family of pro-inflammatory cytokines that includes interleukin 1 alpha (IL-1) and interleukin 1 beta (IL-1), as well as an anti-inflammatory drug called interleukin 1 receptor antagonist (IL-1Ra or IL-1RN) [(3)].

Interleukin 1 beta (IL-1 β) is an inflammatory response regulator that is produced in response to infection, damage, and antigenic exposure. It's involved in autoimmune disorders including rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes, as well as diseases like atherosclerosis, chronic heart failure, and type 2 diabetes that are linked to the metabolic syndrome [(4)].

Interleukin 1 beta (IL-1β) has been a known mediator of beta-cell dysfunction and death and is potentiated by Tumor Necrosis Factor (TNF-α) and Interferon Gamma (IFN-g), both of which are present at high levels under conditions of insulin resistance. Indeed, beta-cells are uniquely susceptible to interleukin 1 beta's effects as they express higher levels of interleukin 1 receptors (IL-1R1) than any other cell type in the body [(5)]. And their subsequent activation resulting in direct promotion of apoptosis, as well as the inhibition of insulin signaling, which is critical for optimal beta-cell function [(6)]. In addition, interleukin 1 beta (IL-1β) signaling results in the production of pro-inflammatory mediators that act in a feed-forward autocrine/paracrine manner in beta-cells and local innate immune cells to amplify these effects [(7)].

AIM OF THE WORK

The aim of this work is to assess the role of interleukin 1β, in patients with type 2 diabetes mellitus (controlled and uncontrolled) compared to healthy individuals.

PATIENTS AND METHODS

A case control study was conducted on patients attending the endocrine clinic at Ain-Shams University Hospital from November 2014 till November 2016 on eighty (80) subjects; their age ranged from 40 to 60 years. The subjects were divided into 3 groups: Group (1) 30 recently uncontrolled type 2 diabetic patients on sulphonylureas over last 6 months their FBS>130, 2 hrs pp>180, HBA1C≥ 7, Group (2): 30 controlled type 2

Received: 05/08/2021
Accepted: 01/10/2021

diabetic patients on sulphonylureas over last 6 months their FBS<130, 2 hrs pp<180, HBA1C<7, Group (3): 20 healthy individuals FBS<100, 2hrs PP<140, HBA1C <5.7.

Exclusion Criteria: included all patients with chronic liver or renal disease, patients with any organ failure, malignancy or evidence of inflammatory or autoimmune diseases and patients kept on metformin and thiazolidinediones**.**

All patients were subjected to full medical history emphasizing on age, onset and duration of diabetes, thorough clinical examination including body mass index (BMI) measurement.

Laboratory studies: included fasting, two hours postprandial blood glucose level, glycated hemoglobin (Hb A1C), lipid profile including total cholesterol, triglycerides, low density lipoproteins, high density lipoproteins, fasting insulin, HOMA IR and serum interleukin-1 beta.

Ethical approval:

The study was registered and approved by local institutional committee of Ain Shams University Hospital and all procedures were in accordance with standards of 1964 Helsinki Declaration and its later amendments ethical standards. Informed consent was obtained from each participant included in the study.

Statistical analysis

After the collection of data, revision and tabulation; analysis was performed using Predictive Analytics Soft Ware (PASW) version 18. Quantitative parametric data were expressed as mean ± SD. Qualitative data were expressed as number and percent of total. Comparative analysis was done using one-way ANOVA and Chi square tests for quantitative and qualitative data respectively. Correlations were done with Pearson's correlation coefficient. P value less than 0.05 was considered significant.

RESULTS

On comparing demographic, clinical and laboratory data among the different studied groups there was a significant difference as regards BMI, fasting blood sugar, 2 hours post prandial blood sugar, lipid profile, fasting insulin and HOMAIR between group of uncontrolled diabetic patients and controlled diabetic patients (Table 1).

Table (1): Comparison of demographic, clinical and laboratory data among the studied groups

	Recently uncontrolled diabetics (Group 1)	Controlled diabetics (Group 2)	Control (Group 3)	P-value
Age (years)	55.767±7.001	52.700±7.778	52.523±7.571	0.193
BMI (Kg\m^2)	27.530±2.613	25.265±3.127	25.835±2.799	**0.009**
SBP (mmHg)	124.689±7.303	123.00±9.154	125.003±5.130	0.588
DBP (mmHg)	77.667±6.261	76.500±6.309	78.002±6.959	0.666
FBS (mg\dl)	198.033±32.762	95.533±9.853	87.550±9.035	**<0.001**
2hr PP (mg\dl)	258.076±39.253	113.534±10.441	107.150±4.196	**<0.001**
HbA1C (%)	8.991±0.991	5.861±0.637	4.941±0.472	**<0.001**
Cholesterol (mg\dl)	215.733±49.228	184.103±14.162	146.602±25.527	**<0.001**
TG (mg\dl)	210.503±48.373	152.803±17.385	127.503±31.808	**<0.001**
LDL (mg\dl)	137.843±20.765	144.001±13.622	132.250±8.451	**0.039**
HDL (mg\dl)	42.004±6.335	46.967±3.882	45.050±3.942	**0.129**
F. Insulin (uIU/ml)	36.751±2.556	27.1534.482	13.501±3.323	**<0.001**
HOMA IR	17.502±4.537	7.136±1.413	2.869±0.15	**<0.001**

Comparing serum interleukin one beta (IL-1β) among the studied groups showed a significant difference among the 3 groups (Table 2).

Table (2): Comparison between cases and controls regarding Interleukin 1β (pg/ml)

Groups	IL-1B (pg/ml)	P-value
	Mean± SD	
Uncontrolled diabetic (group 1)	100.000±98.436	
Controlled diabetic (group 2)	22.433±21.286	
Control (group 3)	12.705±9.091	<0.001

Concerning correlation of interleukin one beta (IL 1β) with other data in diabetic studied cases (group 1 and group 2); there was significant positive correlation with fasting blood sugar (FBS), 2 hours post prandial (2 hrs PP), glycosylated Hemoglobin (HBA1C), triglycerides (TG) and HOMA IR and there was a negative correlation with high density lipoproteins (HDL) and there was no significant correlation with other parameters (Table 3).

Table (3): Correlation between IL 1β and all other parameters in the studied group 1 and group 2 cases

Correlations				
	IL-1B			
	Uncontrolled diabetics (Group 1)		Controlled diabetics (Group 2)	
	r	P-value	r	P-value
Age (years)	0.105	0.582	0.086	0.652
SBP (mmHg)	0.125	0.511	-0.025	0.897
DBP (mmHg)	0.330	0.075	0.055	0.772
BMI (Kg\m^2)	0.091	0.632	0.141	0.456
FBS (mg\dl)	0.449	0.013	0.280	0.135
2hr PP (mg\dl)	0.399	0.029	0.229	0.223
HbA1C (%)	0.272	0.146	-0.118	0.534
Cholesterol (mg\dl)	-0.047	0.805	-0.051	0.788
TG (mg\dl)	0.127	0.504	0.080	0.674
LDL (mg\dl)	-0.152	0.422	-0.065	0.732
HDL (mg\dl)	-0.211	0.264	0.022	0.909
F. Insulin (uIU/ml)	-0.298	0.110	-0.043	0.822
HOMA IR	-0.151	0.425	0.011	0.952

DISCUSSION

In present study, we found serum IL-1β levels were significantly higher in the type 2 diabetic patients than in the healthy control subjects. Also, we found that IL-1β concentrations were significantly higher in uncontrolled diabetic patients than in controlled diabetic patients.

And there was a positive correlation between serum IL-1β concentrations and glycemic profile (FBS, 2 hrs PP and HBA1C) in diabetics generally. Additionally a significant positive correlation was found between serum IL-1β concentrations and glycemic control in uncontrolled diabetics over last 6 months, than in controlled diabetic patients group.

These results are consistent with **Eizadi *et al.*** [8] who measured serum Il-1β concentrations, in 30 type 2 diabetic men patients and 36 healthy subjects matched for BMI, serum Il-1β concentrations were significantly higher in the type 2 diabetics than in the control group.

In the study conducted by **Mirza *et al.*** [9] measuring inflammatory markers; cytokines (IL-6, TNF-α, IL-1β, IL-8) and adipokines (adiponectin, resistin and leptin) among 367 obese and over-weighted Mexican Americans, no significant correlation was found with serum Il-1β concentrations. But this can be explained by low number of diabetic patients among studied population (63 patients 29.7 %). Also it can be explained by ethnic differences since, and according to the study, diabetic Mexican Americans have lower levels of leptin than other ethnics.

Also, **Schumann *et al.*** [10] experimental studies demonstrated that low concentration of IL-1β stimulates insulin release and proliferation in rat and human islets, which is against our study results but this can be explained by the use of different animal models of islets cells and that low concentrations of IL 1β don't have deleterious effects on β cells and that was shown later on by **Maedler *et al.*** [11].

Our study results are also consistent with results from experimental studies done on mice by **Maedler *et al.*** [12] by exposing mice islet cells to increasing levels of IL 1β and the results showed that high concentrations of IL-1β inhibits β-cell proliferation and exposure to 2 and 5 ng/ml IL-1β increased the apoptosis rate by 2.3- and 3.6-fold. Whereas, low concentrations of IL-1β induced β-cell proliferation and had anti-apoptotic effect on islet cells. Exposure to 0.02 ng/ml IL-1β induced a two fold increase in β-cell proliferation compared with controls.

This also agrees with results in our study. In controlled diabetic patients, there were much lower levels of IL-1β concentrations than recently uncontrolled diabetics, which proves that beta cells destruction and hence development of diabetes is related to levels of IL-β. Also it shows that IL-β acts also on beta cells not just peripheral tissues to induce insulin resistance and diabetes.

Hence, No significant positive correlation between serum IL-1β concentrations and glycemic control was found in controlled diabetic patients and even serum IL-1β concentrations were lower.

This can be explained by the inflammatory nature of beta cells destruction in development of diabetes. Many studies have been conducted in order to develop the relationship between various inflammatory mediators and type 2 diabetes mellitus (DM), and have found abnormally high levels of various cytokines, plasminogen activator inhibitor, chemokines, acute phase proteins (such as CRP) in type 2 diabetic patients concluding that high circulating levels of IL-1β, IL-6,

and CRP can be the main predictive indicators for progression of type 2 DM [13].

Many studies also reported the role of IL-1β in beta cell apoptosis and chronic inflammation; it is reported that increased secretion of IL-1β have been linked not only to various autoimmune and auto-inflammatory diseases, but also to metabolic dysregulation [14] and a disturbance in its secretion is associated with type II diabetic and impaired beta cell function [15,16]. IL-1 β, rather than being immediately cytotoxic, may cause tissue inflammation in type 2 diabetes, affecting both beta cell functional mass and insulin sensitivity [17]. In addition to impaired insulin secretion, IL-1β was found to induce β -cell death, which was potentiated by TNF-α [16].

The effects of IL-1β on β-cells of pancreas can be also demonstrated by the clinical trials using IL 1β antagonist (Anakinra); According to the findings of a study by **Dinarello** [18], suppressing IL-1beta-mediated inflammation in the islet microenvironment by blocking its receptor with anakinra or neutralising anti-IL-1beta antibodies is sufficient for correcting dysfunctional beta-cell insulin production in type 2 diabetes, including the possibility that suppression of IL-1beta-mediated inflammation in the islet microenvironment allows for regeneration.

Larsen *et al.* [19] conducted a double-blind, parallel-group trial involving 70 patients with type 2 diabetes, 34 patients were randomly assigned to receive 100 mg of anakinra (a recombinant human interleukin-1-receptor antagonist) subcutaneously once daily for 13 weeks and 36 patients to receive placebo at baseline and at 13 weeks. At 13 weeks, in the anakinra group, the glycated hemoglobin level was 0.46 percentage point lower than in the placebo group (P=0.03); C-peptide secretion was enhanced (P=0.05), and there were reductions in the ratio of pro-insulin to insulin (P=0.005) and in levels of interleukin-6 (P<0.001) and C-reactive protein (P=0.002). And they concluded that the blockade of interleukin-1 with anakinra improved glycemia and beta-cell secretory function and reduced markers of systemic inflammation [19].

As regards fasting insulin, our study shows a fasting insulin higher in group of recently uncontrolled diabetics than in controlled diabetic patients and controls. There was also a weak negative correlation between IL 1β and fasting insulin among recently uncontrolled diabetic patients.

This is consistent with results of study by **Eizadi *et al.*** [8] which found also a negative correlation between IL1β and fasting insulin among diabetic obese patients that supports the role of IL 1β in insulin secretion of pancreatic beta cells.

However, the study by **Eizadi *et al.*** [8] also showed lower serum insulin in diabetic patients than those of non-diabetics, this can be explained by: In our study, all patients were kept on sulphonylureas as oral hypoglycemic medication, which directly stimulates β cells to secrete insulin; and the negative correlation between IL 1β and fasting insulin appears only in recently uncontrolled diabetics. And this can be explained by gradual destruction and decrease in β cell function by chronic inflammation mediated by IL 1β.

Also as regards HOMA IR our study showed that HOMA IR level higher in uncontrolled diabetics than controlled diabetics or control group. There was also positive correlation between IL 1β and HOMA IR in diabetic population as a whole.

This is consistent to results from studies done by **Ahmadi *et al.*** [20] **and Eizadi *et al.*** [8] who studied serum IL1β levels among obese diabetic patients and normal subjects, and showed higher fasting blood glucose and insulin resistance in diabetic patients compared to non-diabetic subjects, while beta cell function in these patients was significantly lower than those without diabetes .

However and again, study by **Mirza *et al.*** [9] showed no significant correlation between IL 1β and HOMA IR. But this can also be explained by low number of diabetic patients among studied population (63 patients 29.7 %) among the study. Also can be explained by ethnic differences since, according to the study, diabetic Mexican Americans have relatively lower levels of leptin than other ethnics.

As regards cholesterol, the present study showed a significant difference between group of uncontrolled diabetics and controlled diabetics compared to the group of controls.

As regards triglycerides level, there was also significant difference between uncontrolled diabetics and controlled diabetics to the group of controls.

A significant positive correlation was found between serum IL 1β concentration and serum triglycerides (TG) in diabetic studied cases (group 1 plus 2), whereas a significant negative correlation was found with high density lipoproteins (HDL).

In those with visceral obesity, metabolic syndrome, or type 2 diabetes, hypertriglyceridemia is a prevalent lipid abnormality. Hypertriglyceridemia is related with an elevated cardiovascular risk when it occurs in conjunction with low HDL levels and atherogenic tiny dense LDL particles. Insulin resistance is a common underlying characteristic, and increased peripheral lipolysis resulting in increased free fatty acid (FFA) transport to the liver [21].

CONCLUSION

In conclusion our study found that serum IL-1β significantly increased in recently uncontrolled diabetics than controlled diabetics and normal subjects and also serum IL-1β was positively correlated with glycemic levels and control. These results suggest possible role of IL-1β in pathogenesis of type 2 diabetes. So, further studies are needed to clarify the possible role of other cytokines in the pathogenesis of type 2 DM. Also, further studies and trials regarding the use of interleukin one beta antagonist (Anakinra) in treatment and stopping disease progression in type 2 DM.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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