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Original Research Article

Evaluate the IL-33 and SOD In T2DM Iraqi Patients and Its Roles in Disease Development

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ABSTRACT
Background: Diabetes mellitus is a systematic disease associated with increase blood sugar which may occur due to defect with insulin synthesis or their action or both. The current study aimed to evaluate level of IL-33 in T2DM patients. **Materials and methods:** Fifty adult patients diagnosed previously with Type 2 diabetic mellitus, and 40 persons were selected as healthy control group. Age, random blood sugar, and Weight data were collected from all participates, and by using enzyme linked immune sorbent assay two biomarkers were analyze for assessment human IL-33, and SOD concentrations in the serum of both groups. **Results:** The result shown that there was non-significant difference in age and weight of patient group by compare with control. The result of RBS, shown there is highly significant increase in diabetic patient group in comparison with control group. The result parameter IL-33 shown there was significant increase in diabetic patient group in comparison with control group. Finally, there is significant decrease for SOD level in diabetic patient group in comparison with control group. **Conclusion:** The elevation of IL-33 may play a role in T2DM development and could potentially lead to novel therapeutic approaches development.
Keyword: T2DM, IL-33, Cytokines, Diabetic patients

1. Introduction

DM is multifactorial diseases that result in increase the level of glucose more than normal level for long time. A lot of causes associated directly or indirectly with hyperglycemia development. The causes can be category into three class, first class associated with insulin synthesis and production and the second class associated with insulin resistance [1,2], depend on the mechanism of disease development, the common types of DM are type-I DM (Insulin-dependent diabetes-IDDM) and type-II DM (Insulin Independent disease-IIDM) T2DM mainly associated with insulin resistance-IR [1].

DM act as global challenge, in 2014 in United states of America 29.1(9.3%) million persons diagnosed with DM, 86.1 million of population are diagnosed with prediabetes, and 40% of population have risk to DM development. Due to systematic effect of DM, the complications of DM associated with problem in kidneys, eyes, cardiovascular system and may be led to death.[3] Due to several published studies, when T2DM Diagnosis in young patients below 40 years old, for unknown causes it associated with more aggressive symptoms and

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complications [4].DM is one of the most global challenges and interfere with quality and duration of life. [5,6]. DM prevalence increases around the world and even the most causes of death which result from renal failure, cardiovascular diseases, and cancer, DM may contribute in their development [7,8]. Therefore, development any protocol can predict DM before occur is valuable in management the disease when occur [9]. One of several factors play role in insulin secretion is Cytokine, Interleukin-33 (IL-33) is one of them which consider one members of IL-1 family is an alarmin cytokine, has a role in regulate TH-2 immune responses and metabolism [10]. Their production occurs pancreatic islets via mesenchymal cells and has direct role in stimulate insulin secretion. Therefore, IL-33 has direct effect on islet -cell function [11]. Therefore, the aim of study designed to study role of IL-33 in development Type 2 DM in Iraqi patients.

2. Materials and Methods

Study Protocol

Fifty adult patients diagnosed previously with diabetic mellitus, and 40 persons were selected as healthy control group in this study. The patients were continuously visitors to Najaf Diabetes and Endocrinology Center in Al Sader medical city. There are some data obtain : Age , random blood sugar (RBS) two hours after last meal, Weight, and by using enzyme linked immune sorbent assay(ELISA)two biomarkers was analyze by (Fuji Dri –chem German) for assessment human IL-33, and SOD concentrations in the serum of both groups according to prepare processed from Bioassay Technology Laboratory, China-Cat-No. E0044Hu, and E0918Hu respectively the test achieved in Al-Ameen center for research and advanced biotechnology in Najaf.

Inclusion and exclusion criteria

Only Iraqi patients with T2DM were inclusion in the current study, while any patients with another type of DM, Autoimmune diseases, and any types of inflammations were excluded.

Blood Tests

Blood collection, it is collected and placed in a test tube including at room temperature and then used for getting RBS also blood collection and placed in gel tube then leave for 30 minutes in room temperature by centrifugation at 3000 rpm for 15 min serum separated and placed in Eppendorf tubes kept at freezer in _20, until used for IL-33, and SOD concentrations assessment.

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Statistical Analyses

The data were analyzed using version 26 of the Statistical Product and Service Solutions (SPSS) software. Qualitative data were expressed as percent and numbers. The data's normality were determined by utilizing Kolmogorov-Smirnov-test, The results were expressed as the Mean along with the standard deviation (S.D), Student t-test to determine statistical significance (P-value < 0.05).

3. Results and Discussion

Interleukin-33 (IL-33), a cytokine of the IL-1 family, plays a pivotal role in the immune-inflammatory responses associated with type 2 diabetes mellitus (T2DM). Its molecular expression is notably dysregulated in T2DM patients, often correlating with chronic low-grade inflammation and insulin resistance. IL-33 acts through its receptor, ST2, influencing pathways that exacerbate metabolic dysfunction, including the activation of macrophages and T-helper type 2 cells. Elevated IL-33 levels in T2DM patients have been linked to increased adipose tissue inflammation, oxidative stress, and impaired glucose metabolism. This dysregulation underscores IL-33's potential as a biomarker for disease progression and a therapeutic target for mitigating diabetes-associated complications. [9.11].

DM is a chronic state result from defect in production of insulin or defect in the body's response to insulin or/and both, leading to persist distribute glucose metabolism. About half billon persons with age ranged 20 to 79 years are affected by DM around the world. The reports refer to this ration will arise in 2030 to comprise 643 million individuals, and in 2045 the ratio will arise to 783 million individuals [12].

Also, the IDF reported that the prevalence of DM in 2017 was 425 million persons around the world, and this prevalence will increase to 629 million persons in 2045 [13]. Around the world, T2DM considered from diseases associated with Middle Ages, although their prevalence increased recently at younger ages [14, 15]. Among several factors causing the deaths, T2DM comprising about 8.4% of these causes, and this ratio represent significant healthcare resources [15].

The result of this study show that diabetic patients ages were highly significant in comparison with control group and this may be explained due to that patients came to diabetic center when they at late stage when the harmfully symptoms, and other complications of this disease is develop forward and this agree indirectly with our ages in both groups because patients with DM at old ages more probably to have high risks to cardiovascular diseases when compared with younger ages[16]. Identifying the ages of patients with DM may be give chance to identifying who patients with more likely to have complications, and this led to good DM management with more effective treatment regimens. Also, by using the public health measures, the onset of the T2DM can be delayed this meaning reduce the duration of disease, and decrease the chance of complications development [17]. However, many reports refer to younger patients with T2DM have bad control on glucose level and low attention to treatments protocols by compared with older patients. [18]. In general, the risk to T2DM development

increase with advance in ages, In the developed countries, high incidence of T2DM diagnosed with old people (about 65 years), while in the developing countries most patients recorded with ages arranged 45 to 64 years. These differences belong to population composition variations between developed and developing countries [19].

The weight result of current study shows there is non-significant difference ($p > 0.05$) in diabetic patient group when compared with control group and this agree and disagree with some studies. Some reports shown the weight is increased in patients with intensive glycemic control [20,21]. Other studies attempt to explain these facts, suggest the weight increased due to effect of improving glycemic control that led to decrease glucose excretion in urine (energy saving), [22], another study suggest poor controlled DM led to catabolic inhibition.[23]. In addition, the insulin anabolic effects can be led to increase fat deposition [24] and protein anabolism [25]. All these effects led to hepatic glucose production inhibition and gluconeogenesis finally led to reduce energy expenditure [26].

Due to psychological factor that results from fear of DM patients from hypoglycemia lead them to large food quantity intake and lead finally to weight gain [27]. Current study agrees with study conducted by Abd and Al- Jumaili 2022, That showed there was non-significant difference between Body Mass Index (BMI) in patients with T2DM and healthy control group [28]. This controversial relationship may be due to different effect that related to sex, hormones, country, genetic, and medication used to deal with diabetic mellitus due to according to our knowledge there is negative correlation with body weight also in some studies.

Table (1): characterization of diabetic patient groups. Showed age, Weight, random blood sugar (RBS) (mg/dl), serum Interleukin-33 (IL-33) (pg/ml), and Superoxide Dismutases (SOD)(ng/ml), Mean ± S.D, S.E significant differences ($P< 0.05$) between means.

Group Statistics						
	Groups	N	Mean	S.D	S.E	Sig. level
RBS	controls	40	97.500	3.7193	1.1762	.002
	Patients	50	236.233	132.7707	24.2405	
Age	controls	40	45.700	11.0836	2.5563	.808
	Patients	50	58.900	13.3348	2.4346	
Weight	controls	40	74.40	14.408	4.556	.769
	Patients	50	72.73	15.774	2.880	
IL33	controls	40	175.290	34.7914	15.5592	.001
	Patients	50	520.062	128.8452	28.8107	
SOD	controls	40	135.267	19.6565	6.2159	.016
	Patients	50	97.683	45.1813	8.2489	

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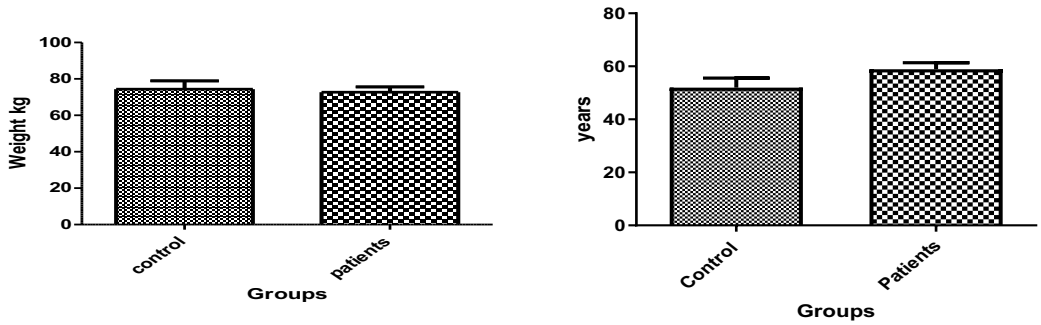
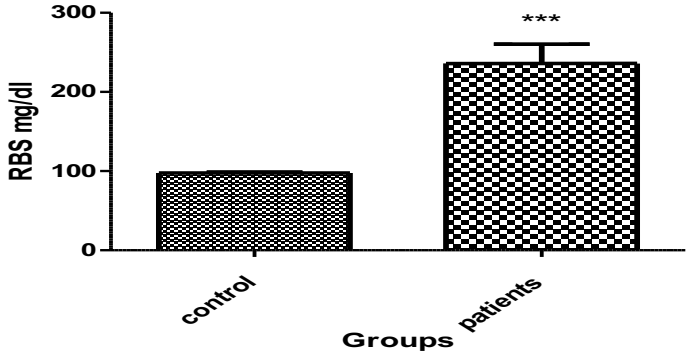


Figure (1): Show Age years and weight Kg in groups; control, and diabetic patients

The result of RBS (mg/dl) tests in current study observed that blood glucose concentration was higher in T2DM patients when compared with control group (236.233 ± 132.7707), (97.500± 3.7193) respectively($p < 0.05$), as shown in figure 2. This finding agrees with a study revealed a hyperglycemia occur in T2DM patients when compared with controls. The risks of DM development arising with advance in age and results from problem(s) associated with insulin synthesis, secretion, and/or action. [28,29]



Figure(2): Show RBS mg/dl in groups; control, and diabetic patients group.

The result of biological parameter IL-33 (pg/ml) show there is significant increase of IL-33 level in diabetic patient group when compared with control group respectively (520.062± 128.8452) ,and (175.290± 34.7914), ($p < 0.05$) as shown in figure 3. These finding in agreement with the study that suggest T2DM patients associated with IL-33 protein expression in subcutaneous adipose tissue more than control, and this likely linked with insulin resistance (IR) and decrease level of gene expression associated with lipid storage. Also IL-33 may be aid in glucose uptake by adipocyte [30].

The findings of current study consistent with several previous reports found, IL- 33 expression increased in obesity patients and metabolic disorders such as DM [31-33]. While another study found that obese patients unital without T2DM, have high level of IL- 33 ,when compared with the patients have obesity and T2DM together, and control group[34]. However, IL-33 level in circulation and adipose tissue are not always consistent. IL-33 is continuously

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made by some cells in liver, GIT, and blood vessels such as fiber producing cells (fibroblasts), endothelial, and epithelial [35].

Several studies shown mRNA IL-33 expression in adipose tissue, and their expression has negative action on expression several other genes associated with lipogenesis, and adipogenesis. This suggests that an increase in IL-33 level in T2DM patients associated with reduce adipose tissue ability to fat storage, and also gene expression of IL-33 reduce the ability of adipose tissur to glucose uptake through interfere with expression of other genes associated with insulin signaling such as Glucose transporter 1, and 4.[36]

The inhibitory effect was indicated at physiological levels of IL-33, like to those shown in patients with obesity [37]. Furthermore, in vitro studies shown when IL-33 incubate with human adipose tissue result in decrease in level of mRNA GLUT4 expression, and at same time the level of AKT stay without any change when insulin exposure. Thus, the inhibitory effects of IL-33 on uptake of glucose associated with decrease level of mRNA GLUT4 expression, rather than alterations in insulin signaling. This study highlights the regulatory role of IL-33 in glucose uptake via adipose tissue. Contrary to previous findings in mice, the results do not indicate what support a protective role of IL-33 in metabolism of glucose in adipose tissue [38].

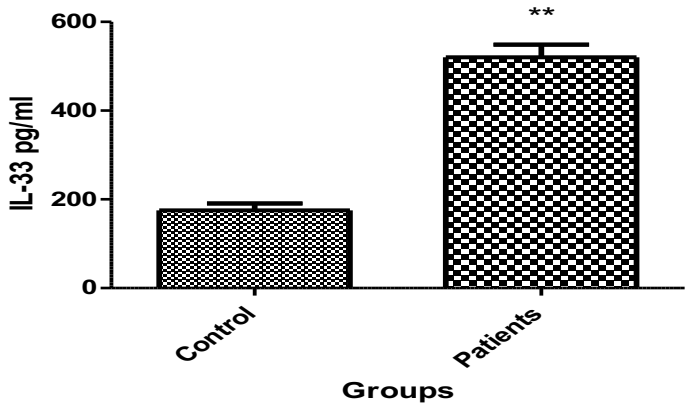

Figure (3): Show IL-33 pg/ml in groups; control, and diabetic patients' group

Also there is significant decrease ($p < 0.05$) for SOD (ng/ml) level in diabetic patient group in comparison with control group respectively (97.683± 45.1813) , and (135.267± 19.6565), as shown in figure 4. Current evidence supports the role of oxidative stress in the pathogenesis development in T1DM and T2DM. In diabetes, free radical generation occurs through non-enzymatic glycation of proteins, oxidation of glucose, and increased lipid peroxidation, all these processes lead to enzyme damage, impairment of cellular machinery, and increase chance of insulin resistance because the oxidative stress [39]. Both lipids and the apolipoprotein component of LDL form insoluble aggregates through oxidative processes, particularly hydroxyl(OH^-)radical-induced cross-linkage between apo-B monomers, which contribute in oxidative damage then finally diabetic complications [40].

Mitochondria are the primary sources of oxidative stress. During oxidative metabolism in mitochondria, some of the oxygen used is reduced to water, while the remainder is converted

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into oxygen free radicals (O^-), an important reactive oxygen species (ROS) that can transform into other reactive species such as peroxynitrite, hydroxyl radical, and hydrogen peroxide (H2O2) [41]. Insulin signaling is influenced by ROS and reactive nitrogen species (RNS) in two ways. Firstly, ROS/RNS are produced in response to insulin to facilitate its full physiological function. They also provide a first line of defense against ROS-mediated cell injury by catalyzing the conversion of superoxide, the primary ROS in oxygen metabolism, into molecular oxygen and peroxide. Superoxide is dismutated into less toxic compounds by superoxide dismutases (SODs) [42]. This suggests a decrease in SOD activity in diabetic patients due to its exhaustion from high production rates. However, reports on SOD activity in diabetic patients vary, with some studies indicating an increase [43], a decrease [44], and others showing no change [45].

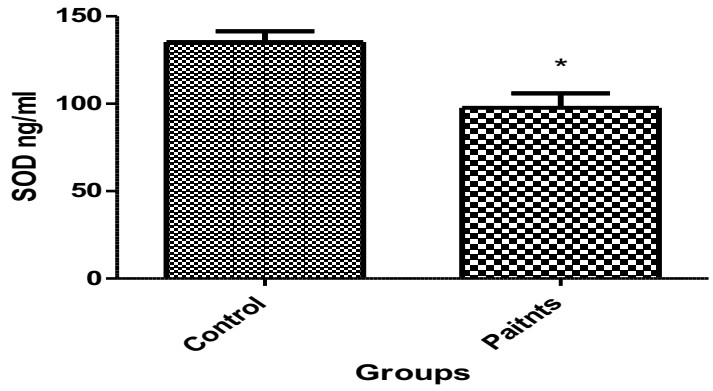

Figure (4): Show SOD ng/ml in groups; control, and diabetic patients group.

4. Conclusions

From current study we can conclude that there is significant differences in diabetic group for RBS, and IL-33 in comparison with control group. In contrast there is no significant effect in Age, weight, and SOD. IL-33 elevation can be explained one of mechanism of T2DM development and may be hive an entrance to novel therapeutical protocol development.

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