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ORIGINAL ARTICLE

Immune Involvement in Diabetes Mellitus: Analysis of TLR4 and ICE Serum Levels in Patients from Basrah

[1]Haneen H. Qasim, [2]Maysaloun AL-Sadoon*, [3]Saad S. Hammadi
[1]Department of Anatomy, College of Medicine, University of Basrah
[2]Department of Microbiology, College of Medicine, University of Basrah
[3]Department of Internal Medicine, College of Medicine, University of Basrah

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Corresponding Author:
Assist. Prof. Maysaloun AL-Sadoon
Department of Microbiology, College of Medicine, University of Basrah
Tel: +964 770 002 9029
maysaloon.nasseir@uobasrah.edu.iq

ABSTRACT

Background: *Diabetes mellitus (DM) is a prevalent chronic metabolic condition that is linked to increasing rates of illness and death globally. Recent findings suggest a role for innate immunity, particularly Toll-like receptor 4 (TLR4), in the development of DM.* ***Objective:*** *This research seeks to explore the involvement of Toll-like receptor 4 (TLR4) and pancreatic islet cells in the onset and advancement of diabetes mellitus.* ***Methodology:*** *A case-control study was undertaken at FDEMC, Basrah, Iraq between May 2022 and August 2022, including a total of 169 participants (98 diabetic patients and 71 age and sex-matched healthy controls). The levels of TLR4 and ICE in serum were analyzed by ELISA. Statistical analysis was conducted using SPSS v26, with significance set at $p < 0.05$.* ***Results:*** *No notable differences were observed in the age or sex distribution of the two groups. The duration of T2DM was longer in comparison to T1DM (8.61±6.14 vs. 5.57±4.02 years). T1DM patients were predominantly underweight (51%) and T2DM patients were predominantly obese (63.3%) with a difference in BMI being significant ($p=0.011$). The levels of TLR4 and ICE were found to be significantly elevated in individuals with diabetes compared to those in the control group ($p<0.0001$), especially among participants aged 21 to 30 and in females.* ***Conclusion:*** *The higher TLR4 and ICE levels in diabetic patients, particularly in younger age group and females, substantiate their participation in immune-mediated connections tied to the onset and advancement of diabetes. This connection underscores the intricate role these markers play in the disease's landscape.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder known as a major cause of mortality in adults. It is either due to a lack of, or ineffective, production of the hormone insulin by the pancreas known as T1D, or the body's tissues resisting the action of the hormone, known as T2D [1]. This interference with insulins action causes the blood glucose to be too high. Over time, high blood sugar can cause damage and/or malfunction of the liver, kidneys, retina of the eyes, nerves, blood vessels and the heart [2].

Overall, approximately 463 million people from 20 to 79 years of age, suffer from diabetes globally, as reported by the International Diabetes Federation, which indicates a significant public health problem [3]. Out of these, 90% suffer from Type 2 Diabetes Mellitus (T2DM) and the number is estimated to reach 700 million by 2045. Equally alarming; however, is the fact that nearly 50% of patients with diabetes (i.e., 232 million) are still undiagnosed, with more than 374 million people diagnosed with prediabetes (83% of whom will most likely develop T2DM in the future). Therefore, type 2 diabetes has become an important and growing public health problem globally [4].

The autoimmune illness type 1 diabetes mellitus (T1DM) arises from the adaptive immune system selectively targeting pancreatic β-cell antigens. But the innate immune system also is responsible for initiating and maintaining the adaptive immune response, which includes B and T cells[5]. TIIDM is characterized by insulin resistance, glucose intolerance and chronic hyperglycemia, while T2DM mostly caused by inadequate insulin release, it is typified by elevated blood glucose levels. Innate and adaptive immune processes have been involved in insulin resistance, the main feature of T2DM [6,7].

Recent research highlights the important role of the innate immune system in the induction of chronic sterile inflammation as found in diabetes. This is achieved in part through pattern recognition receptors, particularly Toll-like receptors (TLRs). In humans they have identified 10 TLR (TLR1-TLR10) while mice express 12 TLRs (TLR1-TLR9, TLR 11-TLR13). PAMPs and DAMPs are recognized by these receptors which initiate inflammatory processes. Toll-like receptors (TLRs), which are found in pancreatic islets, may play a

role in the development of various chronic inflammatory conditions, including diabetes [8,9].

TLRs frequently become activated by signaling via adaptor molecule MyD88, resulting in activation of the NF-κB pathway, which induces the production of ROS and pro-inflammatory cytokines. In vitro research has proved that high-glucose culture leads to upregulation of TLR4 and activation of further inflammatory pathways [10]. Remarkably, deletion of TLR4 in mice has been shown to provide protection against some diabetic complications, despite continued hyperglycemia [11].

This research aims to explore the involvement of Toll-like receptor 4 (TLR4) and pancreatic islet cells in the development and progression of diabetes.

METHODOLOGY

Study population

The study involved 169 participants with diabetes who were consecutively enrolled between May 2022 and August 2022. This is case-control analytical research carried out at Faihaa Specialized Diabetes, Endocrine and Metabolism Centre (FDEMC), Basrah governorate, southern Iraq. Two primary groups were formed from the participants: 71 seemingly healthy people matched for both age and sex with 98 patients with T1DM and T2DM as cases. This study was approved by the Ethics Committee of University of Basrah, College of Medicine, Approval Number 2911/39 at 2022/6/23.

Sample Collection

Following the comprehensive history collection from all participants, 5 mL of peripheral blood was aseptically acquired via venipuncture, deposited in a gel tube, and allowed to stand for thirty minutes at room temperature, centrifuged for 5 minutes at 3000 rpm to obtain serum were kept in freeze which was used to detection the levels of TLR4 and ICE. Informed consent was obtained in accordance with institutional guidelines.

Measurements of TLR4 and ICE Levels

The serum levels of TLR4 and ICE were detected quantitatively using the Sandwich ELISA with MyBioSource (San Diego, CA, USA) kits according to kit protocol; cat. no. MBS765181 and MBS702639, respectively.

Statistical Analysis:

SPSS, version 26, was used in performing the data analysis. Assuming normality of continuous variables, data are reported as mean ± SD and median, minimum, and maximum; categorical variables are reported as frequency and percentage. A p-value above 0.05 indicated no significant difference while a p-value less than 0.05 indicated a significant difference. The Chi-square test has been applied for comparing categorical variables wherever applicable; otherwise, Fisher's Exact test has been used. The results Comparisons with continuous, nonparametric variables have been tested by applying the Mann-Whitney U test.

RESULTS

As shown in Table 1, the mean age of patients with diabetes mellitus (DM) was 33.1 ± 20.03 years, next to 35.5 ± 19.9 years obtained in control participants. There were more women than men in both groups, 55.1% (diabetic patients) and 43.7% (controls). The difference between the ratios of genders in the two groups was statistically insignificant ($p > 0.05$). Whereas the high mean value for duration of disease among type 2 diabetic patients (8.61±6.14) when compare with T1DM (5.57±4.02).

BMI of all subject were categorized into four types: underweight, normal weight, overweight, and obese. A majority of T1DM patients were underweight (51.0%) with no significant difference when compare with control group whereas high percent was found within obese in case of T2DM patients represent 63.3% the difference with control group was statistical significance**.**

Islet cells autoantibodies were shown to be high levels among patients with diabetic type 1 and 2 (30.71±20.13**;** 27.69±16.82**)** respectively when compared with theirs control that seen in **Table 2** and Figure **1** Statistical examination revealed statistical significance $P < 0.0001$.

From forty-nine type 1 diabetic patients, high mean levels of TLR4 were observed when compared with their control (39.96±24.83;1.69±1.53) respectively, also high mean levels were detected among patients with T2DM when compared with their control (21.95±9.50; 2.89±1.82) respectively with highly significant differences between two groups **Table 3.**

Those who developed the disease at early ages showed more islet cells autoantibodies and TLR4 than those who developed the disease at older ages with high mean value among age group from 21 to 30 (31.68± 20.14), (44.5±29.9) respectively that shown in **Tables (4,5) and Figures (2,3).** With these markers, statistical analysis revealed significant differences $P < 0.0001$ between patients and controls on these indicators.

Statistical analysis revealed extremely significant differences ($P < 0.0001$) when gender was taken into account: females displayed greater frequency of ICE and TLR4 than males. Table 6.

Table 1: Demographic of the studied groups

Variables		DM (N=98)	Controls(N=71)	P value
Age(years) Mean±SD		33.1±20.03	35.5±19.9	0.454
Gender	Male	44(44.9%)	40(56.3%)	0.169
	Female	54(55.1%)	31(43.7%)	

Disease	Duration of disease	
DM Type 1	N	49
	Mean±SD	5.57±4.02
	Median (Min.-Max.)	5 (1-19)
DM Type 2	N	49
	Mean±SD	8.61±6.14
	Median (Min.-Max.)	8 (0-22)

		Type of diabetes		Total	*P-value*
		Type 1	Control 1		
BMI groups	Underweight	25	10	35	0.172*
		51.0%	32.3%	43.75%	
	Normal	18	21	39	
		36.7%	67.7%	48.75	
	Over weight	5	0	5	
		10.2%	0.0%	6.25%	
	Obese	1	0	1	
		2.0%	0.0%	1.25%	
		Type 2	Control 2		
BMI groups	Normal	5	11	16	0.011**
		10.2%	27.5%	18.0%	
	Overweight	13	16	29	
		26.5%	40.0%	32.6%	
	Obese	31	13	44	
		63.3%	32.5%	49.4%	
Total		49	40	89	
		100.0%	100.0%	100.0%	

* Fisher's Exact Test ; ** Chi-Square Test

Table 2: Distribution of Islet cell autoantibodies among study population

ICE	DM I	DM I Control	DM II	DM II Control
Mean±SD	30.71±20.13	2.76±1.38	27.69±16.82	1.03±0.57
Median (Min.-Max.)	23.78 (10.21-86.66)	2.87 (0.03-6.53)	26.13 (7.98-96.78)	90.87 (0.23-2.98)
P-value*	0.0001		0.0001	

* Mann-Whitney U Test

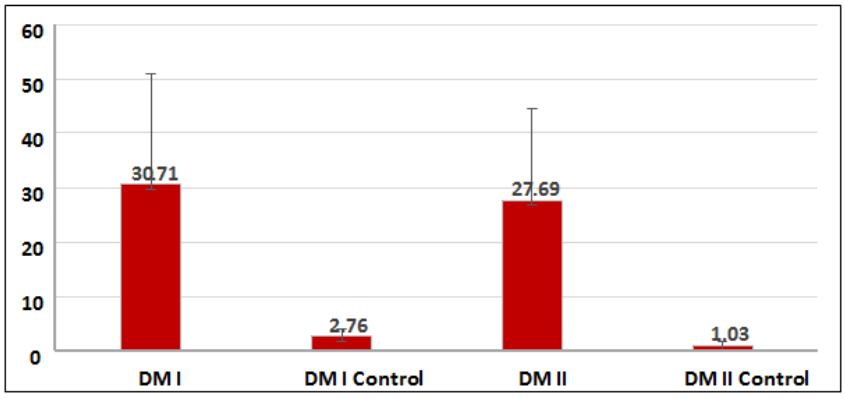

Fig. 1: Distribution of Islet cell autoantibodies among study population

Table 3: Distribution of TLR4 among study population

TLR4	DM I	DM I Control	DM I0I	DM II Control
Mean±SD	39.96±24.83	1.69±1.53	21.95±9.50	2.89±1.82
Median (Min.-Max.)	34.87 (10.78-106.19)	1.22 (0.01-4.98)	20.87 (2.69-45.20)	2.17 (0.34-7.22)
P-value*	0.0001		0.0001	

* Mann-Whitney U Test

Table 4: Comparison of ICE value according to age group among study population:

Age groups (year) of patients		ICE		*P-value*
		Patients	Control	
Twenty years or younger	N	42	24	0.0001
	Mean± S.D	30.2±20.4	2.8±1.45	
	Median	23.3800	2.8700	
	Minimum -Maximum	10.21-86.66	.03-6.53	
From 21 to 30	N	8	8	0.0001
	Mean± S.D	31.68± 20.14	2.3±0.95	
	Median	23.0800	2.4250	
	Minimum -Maximum	18.32-77.65	1.01-3.74	
From 31 to 40	N	7	9	0.0001
	Mean± S.D	25.67±8.62	1.28±0.74	
	Median	26.1300	.9800	
	Minimum -Maximum	11.98- 34.76	.65-2.98	
From 41 to 50	N	15	11	0.0001
	Mean± S.D	24.04±12.49	0.768±0.23	
	Median	20.3200	.7800	
	Minimum -Maximum	8.77-49.87	.43-1.23	
Older than 50	N	26	19	0.0001
	Mean	30.70±20.39	1.0205±0.55	
	Median	27.8350	.9700	
	Minimum -Maximum	7.98-96.78	.23-2.76	

*** Kruskal Wallis H Test**

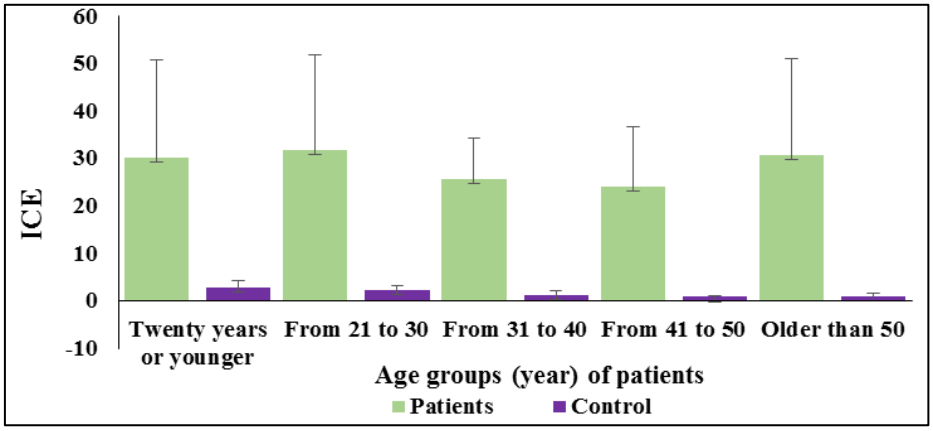

Fig. 2: Comparison of ICE value according to age group among study population

Table 5: Comparison of TLR4 value according to age group among study population:

Age groups (year) of patients		TLR4		*P-value*
		Patients	Control	
Twenty years or younger	N	42	24	0.0001
	Mean± S.D	38.6±23.9	1.5±1.2	
	Median	30.3	1.38	
	Minimum -Maximum	10.78-90.7	0.01-3.98	
From 21 to 30	N	8	8	0.0001
	Mean± S.D	44.5±29.9	2.53±2.1	
	Median	39.78	2.48	
	Minimum -Maximum	15.21-106.1	0.09-4.98	
From 31 to 40	N	7	9	0.0001
	Mean± S.D	18.50±4.8	3.46±1.95	
	Median	18.36	2.87	
	Minimum -Maximum	12.98-25.3	1.41-6.54	
From 41 to 50	N	15	11	0.0001
	Mean± S.D	25.49±8.4	2.38±1.27	
	Median	25.7	2.22	
	Minimum -Maximum	13.09-42.7	0.34-4.44	
Older than 50	N	26	19	0.0001
	Mean±S.D	20.87±10.8	2.85±2.05	
	Median	19.82	2.11	
	Minimum -Maximum	2.69-45.2	0.56-7.22	

* Kruskal Wallis H Test

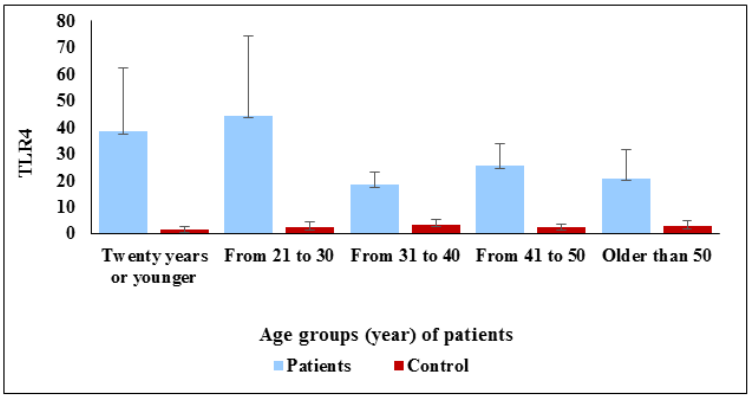

Fig. 3: Comparison of TLR4 value according to age group among study population:

Table 6: Comparison of ICE and TLR4 value according to gender among study population:

Males		ICE	TLR4
Patient	N	44	44
	Mean	26.76	28.39
	Median	23.82	21.07
	Std. Deviation	16.25	19.44
	Minimum	7.98	2.69
	Maximum	86.66	79.10
Control	N	40	40
	Mean	1.89	2.29
	Median	1.23	2.09
	Std. Deviation	1.36	1.32
	Minimum	0.43	0.01
	Maximum	6.53	5.34
P-value*		0.0001	0.0001

Females		ICE	TLR4
Patient	N	54	54
	Mean	31.19	33.04
	Median	23.93	25.50
	Std. Deviation	20.10	21.78
	Minimum	8.76	9.85
	Maximum	96.78	106.19
Control	N	31	31
	Mean	1.65	2.46
	Median	1.21	1.97
	Std. Deviation	1.27	2.28
	Minimum	0.03	0.03
	Maximum	4.42	7.22
P-value*		0.0001	0.0001

DISCUSSION

Diabetes is a significant noncommunicable illness that will provide a major challenge to public health in the Eastern Mediterranean region following the management of infectious diseases and malnutrition. This phenomenon is partly attributable to the fast ageing of people in the developing nations. The prevalence fell within the extensive spectrum of diabetes in the Middle East [12].

The purpose of this study is to examine the role of toll-like receptor 4 and pancreatic islet cell autoantibodies in type 1 and type 2 diabetes patients in comparison to the corresponding control groups.

The results gathered in this study indicate that patients' mean age with diabetes was 33.1±20.03 years. This conclusion aligns with the results of previous studies conducted by Mahmoud et al. [13], although it is lower than the mean age reported by Sayed et al. [14]. Additionally, the greatest rate of diabetes mellitus was seen in the age group beyond 50 years, at 26.6%. This aligns with the prevalence observed in developing nations, where the largest group of diabetes cases is amongst 45–64-year-olds [15].

In our study, just over half of the patients were female. This percentage is greater than that stated by Almogbel *et al.* [16] and Sayed et al. [17], that only 19% and 17% of their participants were women. However, it is still lower than the percentage reported by Odetti *et al*. in Italy[18]. There might be a few reasons why women made up the bulk of the study's participant s. First, diabetes mellitus (DM) is a little more common among women in our community, as reported by Mansour et al. [19]. Second, the nature of the population seen at this medical center may be a contributing factor. Many of the women who sought treatment were housewives, and they may have more flexibility during the day to visit clinics, contrast to men, who are typically full-time workers.

The body mass index (BMI) is a widely used indicat or of overall obesity and related metabolic complications. Several studies have shown a strong link between being overweight and a higher risk of death—ranging from 40% up to 300% greater than in individuals with a normal BMI (20,21). Gray et al. [22]also highlighted that being overweight and physically inactive are important risk factors for type 2 diabetes mellitus and many other chronic disorders (T2DM) (22).

The findings revealed that the mean BMI was 24.26±7.20 kg/m² among the diabetic patients. Lower mean BMI values had been reported by Morteza A. et al. [23] and Singh K. et al. [24]. In addition, the mean BMI of diabetic patients in our study was significantly higher than that of control group. This is consistent with the recognized relationship between T2DM and obesity, in large part mediated by insulin resistance. Obesity, on the other side, is the consequence of several risk factors to which overeating, physical inactivity, hormonal balance, genetic factors and others are related as causative factors [25].

In an analysis of forty-nine type 1 diabetes patients, the prevalence rates of autoantibody ICE and TLR4 were (30.71±20.13, 39.96±24.83), respectively. Significant high frequency of the antibodies was found in the Type 1 diabetes patients according to their controls ($p<0.001$). This result is consistent with the results reported in previous study of Laadher et al. [25] and Belhiba et al. [26,27] These findings indicate that islet cell autoimmunity plays a substantial role in the aetiology of the disease, and provide clarification that of autoimmune diabetes, that is type 1, is still more common than idiopathic type. Nevertheless, these findings seem to surpass that of the Saudi Arabian and one Taiwanese studies of type 1 diabetic patients. Damanhouri et al.[28]; Chang et al. [29].

The disparities in the incidence of these autoantibodies may be ascribed to variations in the assays employed, variances in procedural sensitivity and the genetic or environmental features of the individuals. It was discovered that people who got the condition during infancy and early puberty had higher prevalences of these autoantibodies, and that as age increased, the prevalence started to decline.

Patients with type 1 diabetes had mean ICE levels of 30.71±20.13, whereas those with type 2 diabetes had mean ICE values of 27.69±16.82. These findings concur with several studies [30,31] that showed that the prevalence of islet cell autoantibodies decreased as the age of onset increased. These studies also reported autoantibodies are more prevalent in individuals who develop the disease in childhood and younger age groups. This may be ascribed to hereditary and non-genetic variables that affect the existence of disease-associated antibodies, the pace of development to clinical onset of diabetes, and the severity of diminished insulin secretion capability [32]. Children with type 1 diabetes mellitus exhibit a high prevalence of heterozygous alleles, placing these patients at an elevated risk for autoantibodies. Consequently, antibodies appear to be more common in this age demographic, and as the proportion of heterozygous alleles diminishes with age in insulin-dependent diabetes mellitus, the prevalence of autoantibodies also decreases [30].

Environmental factors such as early exposure to cow's milk, reduced duration or absence of breastfeeding, insufficient vitamin D intake, and early introduction of cereals have been associated with the development of autoimmune diabetes as age-related non-genetic contributors [31]. Therefore, loss of genetic or environmental influences in this age group may be the reason of the notable post pubertal drop in illness incidence [27].

This study revealed that, generally speaking, women were more impacted by diabetes mellitus than men. Females also had a greater prevalence of islet cell autoantibodies (ICE) than males, despite the fact that the gender distribution difference in ICE is statistically non-significant.

This finding aligns with what was demonstrated by other studies [32,33], which identified an increased frequency of islet cell reactivity among females compared to males. However, another study demonstrated no correlation between gender and autoimmunity in diabetic patients [31]. This finding can be explained by the observation that autoimmune diseases occur more frequently in females than in males. A plausible reason for this disparity may be the influence of sex hormones, which could lead females to have a heightened response to conventional antigens [34].

CONCLUSION

More investigation is warranted on how gonadal steroids interact with the immune system The sex hormones may influence the genetic regulation of auto antigen presentation to T lymphocyte by specialized cells. Human immune responses are known to exhibit sexual dimorphism; females are more resistant to numerous infections, have more robust cellular and humoral immune responses, and experience a higher prevalence of autoimmune disorders than men.

Additionally, the illness presentation of women appears to be determined by their reproductive status. Exacerbations may occur during particular menstrual cycles or during pregnancy in patients with immune-based conditions like Multiple sclerosis (MS), asthma, or systemic lupus erythematosus (SLE) can have flare-ups of the condition in specific phases of the menstrual cycle or during "child bearing" (e.g., during pregnancy). It is the differences in sex hormones that lead to the differences in immune responses between the sexes and in women during the reproductive phases. Therefore, it has been postulated that the differences in sex hormone levels mediate these sex specific immune responses. The effects of reproductive hormones are very complex.

We affirm that the submission represents work that has not been published previously and is not currently being considered by another journal. Also, I confirm that each author has seen and approved the contents of the submitted manuscript.

Conflict of Interest: The authors declare that they have no conflict of interest

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