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The Association Between NLRP3 and the Development of Depression in Type 2 Diabetes Patients

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ABSTRACT

Background: *Type 2 diabetes is a chronic disease characterized by two characteristics: insulin resistance and destruction of pancreatic beta cells, leading to high blood sugar levels. This disease is associated with many complications that can be serious and life-threatening, such as depression. The presence of inflammatory components like inflammatory cytokines and immune protein complexes in high concentrations in the blood of type 2 diabetes patients has led to theories and studies that support the involvement of certain inflammatory pathways in the relationship between these two diseases.* ***Method:*** *This cross-sectional study included the selection of 128 individuals diagnosed with type 2 diabetes from the Diabetes and Endocrinology Center located in Najaf, Iraq from August 2023 to October 2023. The study included 43 men and 85 women. The ages of the participants ranged from 30 to 75 years. Patients were randomly selected during their visit to the center.Depression was diagnosed using the Hamilton scale, a blood serum sample was taken, and the NLRP3 level was measured using the ELISA device.* ***Result****: The results ultimately showed that inflammasome levels were higher in people with depression than in patients with type 2 diabetes than in patients with diabetes who did not have depression, and the difference was statistically significant p-value (0.020).*

Keywords: Insulin Resistance, Inflammatory Cytokines, Chronic Disease, Depression, Inflammasome.

Article Information

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INTRODUCTION

Type 2 diabetes (DM) is a metabolic disease that is a lifelong ailment that is affecting an increasing number of people worldwide[1]. Individuals with type 2 diabetes either produce insufficient amounts of insulin or have insulin resistance, which prevents the cells from using glucose as an energy source [2]. Type 2 diabetes is classified as an inflammatory immune disease. Inflammation and dysfunction of immune cells play a role in causing insulin resistance and a defect in insulin production by causing damage to the beta cells of the pancreas[1][3][4]and the type 2 diabetes mellitus (T2DM) also is well recognized as a chronic inflammatory condition characterized by elevated levels of tumor necrosis factor (TNF), interleukins, and adipokines in the bloodstream[5][6].

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Increased thirst, increased hunger, blurred vision, exhaustion, and sluggish wound healing—which can result in recurrent infections—are common symptoms of diabetes. This is because high blood sugar hinders the body's natural healing processes[7]. Type 2 diabetes mellitus (T2DM) is a multifactorial condition characterized by a complicated pathophysiology that involves several tissues and organs. It is influenced by complicated interactions among various factors such as genetic predisposition and various environmental factors[8]. Hence, the inflammatory processes that may be part of the pathogenesis of type 2 diabetes may result in inflammatory cytokines that lead to insulin resistance, stress, and depression through their effect on the nervous system(CNS). Depressive symptoms are present in 12%-27% of diabetes patients, and depression affects a quarter of T2DM patients [9].

Depression is categorized as a psychological condition characterized by sadness and a diminished interest in and enjoyment of activities. Although depression can affect people of any age, young people are the most susceptible[10]. Depression is a disease that has complex environmental, genetic, and physiological factors, can be associated with several chronic illnesses, such as type 2 diabetes, and has negative consequences for the health of patients[11]. Depression is more common in diabetes patients, often misdiagnosed, and both exacerbate each other, affecting self-care and overall clinical outcomes [12]. Certain cells, particularly pancreatic beta cells, possess distinct receptors that get activated under specific circumstances, such as elevated blood glucose levels. These receptors play a crucial role in facilitating the release of insulin and certain inflammatory cytokines by triggering the activation of the NLRP3 inflammasome [13]. The NLRP3 inflammasome is a complex composed of three subunits: NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1 (also known as IL-1–converting enzyme). The enzyme caspase1 is responsible for the conversion of pro–IL–1beta into their fully mature and active forms[14]. The NLRP3 inflammasome serves as a molecular complex that facilitates the synthesis of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) [15][16][17]. The existence of a relationship between these cytokines and stress and depression was confirmed, as levels of IL1β and IL18 were found in the mononuclear cells of depressed patients diagnosed using the Beck scale for diagnosing depression[18].

MATERIALS AND METHODS

Patients' selection

Official approvals were taken from the relevant institutions and approval was obtained from the participants directly and explicitly. This cross-sectional study involved 128 patients, all of whom were diagnosed with type 2 diabetes and were being treated at the Diabetes and Endocrinology Center in Al-Sadr Medical City, Najaf Al-Ashraf- Iraq. The ages of the participants ranged from 30 to 75 years old, and they were asked to complete a special questionnaire containing questions related to their age, history of diabetes, family history of diabetes, level of education, adherence to treatment, and marital status.

The level of NLRP3 in the blood serum of all participants was measured using an ELISA device (Sunlong, China), and then all data were collected and analyzed using the statistical package for Social Sciences Programme (SPSS) Version 26, developed by Inc in Chicago United States of America. participants underwent depression screening using the Hamilton Depression Scale, and a comprehensive interview was conducted with each patient.

Inclusion criteria:

- Patients with type 2 diabetes were diagnosed by performing basic tests to diagnose diabetes, such as fasting blood sugar and HbA1C, and confirming the diagnosis by the center's specialist.

Exclusion criteria:

- Type 1 diabetes patients
- Pregnant women with gestational diabetes
- Pre-diabetic patients

RESULTS

Out of these 128 patients with T2DM 32 (33%) were detected to have mild depression, 33(34.02%) moderate, 17(17.52%) severe, and 15(15.46%) had very severe depression, The remaining 31 (24.2%) did not exhibit any depressive symptoms. there is a significant difference in p-value of (0.002) between the two groups in the (male and female groups), DM without depression 31 patients, 18(58.1%) were male and 13(41.9%) were female, DM with depression97 patients, male 25(28.5%), female 72(74.2%). The difference in ages between the two groups of people was not statistically significant, the p-value was (0.516). Similarly, there was no significant difference in the mean age of patients with and without depression. The mean age for those without depression was 53.70±9.93years, and for those with depression, it was 53.64±8.90years, with a p-value of (0.975). According to diabetes duration, marital status, participants' education level between the two groups there was no statistically significant difference, the p-value were (0.166, 0.545, 0.514) respectively, additionally, the family history and treatment adherence didn't show here is statistically significant difference between the groups. The obtained p-value were (0.646, 0.116) respectively. The mean FBS and HbA1c of DM patients with and without depression don't reveal statistically significant difference in these values between the two groups' p-value (0.687, 0.741).

Comparison of NLRP3 biomarkers among the studied groups revealed a significant difference in p-value (0.020) in the mean level of NLRP3 across the studied groups of DM without depressed (58.78±25.52 pg/) and (71.80±27.23 pg/ml) in DM patients who were depressed. Comparison of NLRP3among the studied groups revealed a significant difference, when compared the mean of NLRP3 for non-depressed (58.78±25.52 pg\ml) with the mean of moderate depression (72.41±. 24.48 pg\ml), the p-value was (0.046) and when compared with the mean for very severe depression (78.15±28.71 pg\ml), the p-value was (0.024), compared to the mean for mild depression and severe depression (68.44±31.81 pg\ml, 71.37±22.55 pg\ml), the result was statistically insignificant, and the pvalue was (0.159, 0.125) respectively.

Table 1: Demographic Characteristics of the studied groups.

Sociodemographic characteristics		Scores of depression severity					P value
Age group (Year)	Mean±SD	No Depression		Depression			0.975
		53.70±9.93		53.64±8.90			
		No Depression	Mild	Moderate	Severe	Very severe	
	<50	9 29.0%	10 31.3%	12 36.4%	4 23.5%	4 26.7%	0.899
	50 and more	22 71.0%	22 68.8%	21 63.6%	13 76.5%	11 73.3%	
Sex	Male	18 58.1%	12 37.5%	6 18.2%	1 5.9%	6 40.0%	0.001
	Female	13 41.9%	20 62.5%	27 81.8%	16 94.1%	9 60.0%	
Social	Married	29 93.5%	32 100.0%	32 97.0%	16 94.1%	15 100.0%	0.545
	Widowed	2 6.5%	0 0.0%	1 3.0%	1 5.9%	0 0.0%	
Level of Education	Absent	21 67.7%	25 78.12%	25 75.76%	13 76.47%	12 80.0%	0.514
	Primary school	1 3.2%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	
	Secondary school	4 12.9%	6 18.75%	4 12.12%	4 23.53%	3 20.0%	
	Higher	5 16.1%	1 3.13%	4 12.2%	0 0.0%	0 0.0%	
Onset of disease (years)	<10	14 45.2%	24 75.0%	22 66.7%	7 41.2%	10 66.7%	0.166
	10-15 Count %	14 45.2%	6 18.8%	8 24.2%	9 52.9%	3 20.0%	
	15 and more	3 9.7%	2 6.3%	3 9.1%	1 5.9%	2 13.3%	

Table 2: Biochemical properties of the studied groups.

Parameters	Mean ±SD		
	Nondepressive	Depressive	P value
FBS mg\dl	222.28±128.93 (n=21)	211.25±102.28 (n=67)	0.687
HbA1C mmol\dl	8.52±3.10 (n=15)	8.83±3.13 (n=38)	0.741

Table 3: NLRP3 level in the studied groups.

Marker	Score	Mean pg\ml±SD	Severity	Mean pg\ml±SD	P value
NLRP3	No Depression	58.78±25.52	Depression	71.80±27.23	0.020
			Mild depression	68.44±31.81	0.159
			Moderate depression	72.41±24.48	0.046*
			Severe depression	71.37±22.55	0.125
			Very severe depression	78.15±28.71	0.024*

Table 4: Clinical Parameters in the studied groups.

Clinical Parameter		Depression					P value
		No Depression	Mild	Moderate	Severe	Very severe	
Genetic	**Negative Count %**	**24 77.4%**	**25 78.1%**	**28 84.8%**	**12 70.6%**	**10 66.7%**	**0.646**
	Positive Count %	**7 22.6%**	**7 21.9%**	**5 15.2%**	**5 29.4%**	**5 33.3%**	
Treatment	**regulated %**	**28 90.3%**	**30 93.8%**	**30 90.9%**	**17 100.0%**	**11 73.3%**	**0.116**
	not regulated %	**3 9.7%**	**2 6.3%**	**3 9.1%**	**0 0.0%**	**4 26.7%**	

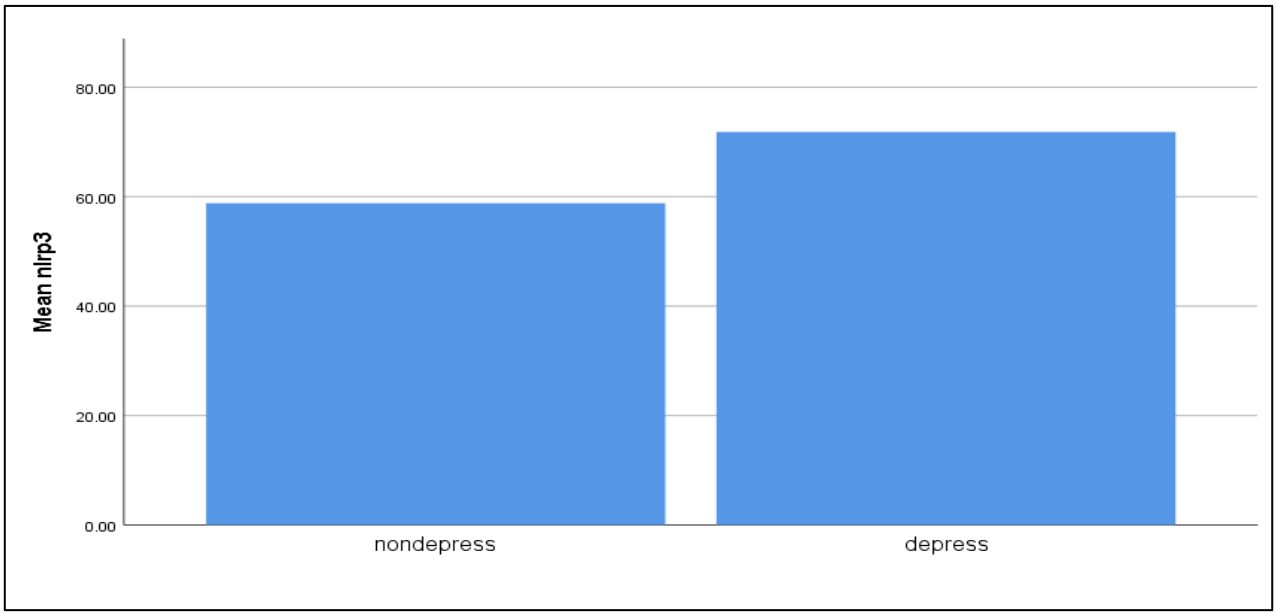

Figure 1: Difference in the mean of NLRP3 levels between the group of individuals diagnosed with depression and the group without depression.

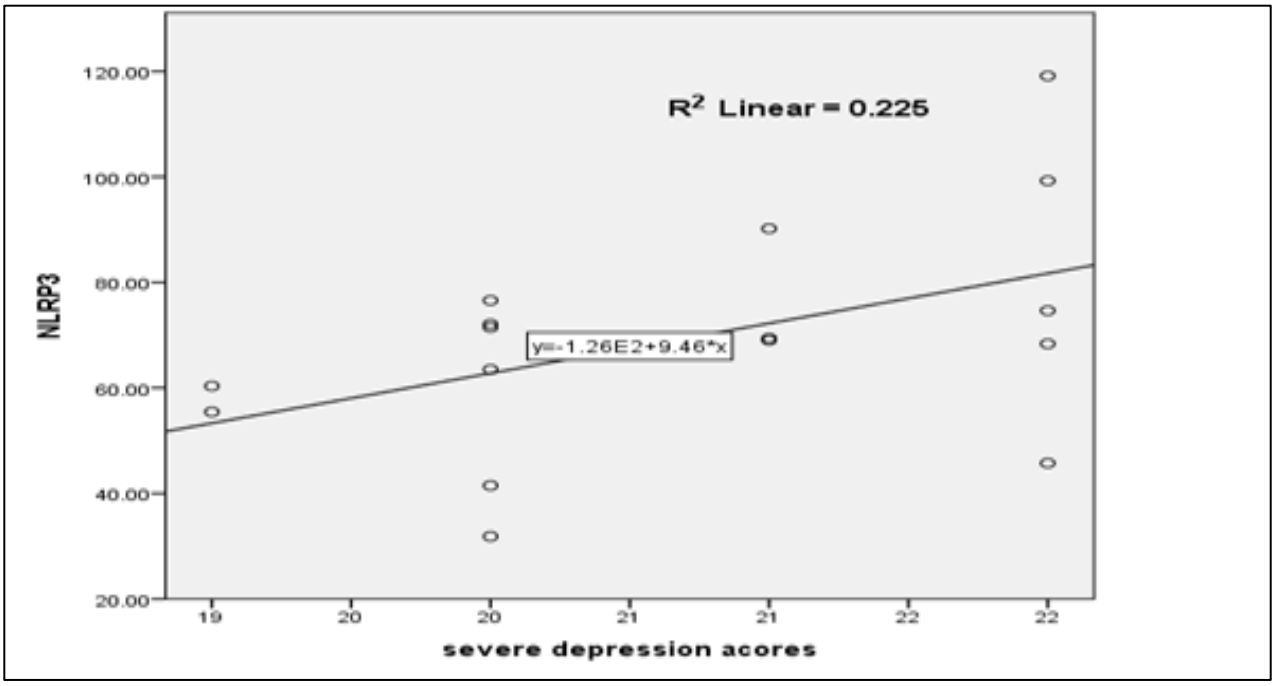

Figure 2: Positive correlation of NLRP3pg\ml with severe depression score Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

In the current study, we investigate the correlation between major depression and serum levels of inflammasome in patients with and without type 2 diabetes mellitus. Consistent with earlier research, serum levels of inflammasome it was evaluated for both groups in this study, the mean concentration of inflammasome in DM suffering from depression was significantly higher with p-value (0.020) (depressed 71.80±27.23, nondepressed 58.78±25.52). A similar pattern of results was obtained by Alcocer-Gómez [19], Li [20], and Xia [21] which confirms the role of the inflammasome in causing depression in diabetic patients and the high concentration in people with depression. It seems possible that these

results are due to the innate immune responses to a variety of stimuli including hyperglycemia, which is the formation of a protein complex called the inflammasome, which triggers a cascade of immune reactions and the production of immune components, including those that act on the pancreas, different cells, and nervous system tissues, among other parts of the body. As a result, the fundamental symptoms of diabetes are accompanied by complications like depression(Iwata et al., 2013; Rovira-Llopis et al., 2018; Li et al., 2021) [20][22][23]. It's interesting to note that there were significant differences were found between DM without depression with DM with (moderate and very severe) depression p-value (0.046, 0.024) respectively. Therefore, it is possible that there is a relationship between the high level of NLRP3 and the severity of depression in diabetics this is consistent with Wang[24] So we believe that these findings are a great starting point for the possibility that NLRP3 will be a helpful marker for tracking depression in T2DM patients.

Studies have shown that the concentration of inflammasomes generally increases in patients with DM type 2 compared to healthy individuals, such as Bae [25]. However, the concentration of inflammasomes became higher in the case of DM type 2 patients with depression, which supports the research hypothesis. When it comes to sex, there was a p-value(0.002), as the number of women exceeded the number of men in the depressed (women72,men25), and this is consistent with Alajmani [26] and Yang [27], which obtained a similar and statistically significant result and well agree with Khaledi[28]which showed that the prevalence of depression in women with type 2 diabetes was higher than in men in different regions of the world.

CONCLUSION

DM type 2 diabetic patients with depression show a significant increase in NLRP3 levels. The detection of varying NLRP3 levels in all patients with type 2 diabetes and the high sensitivity and accuracy of NLRP3 suggest that NLRP3 may be used as a diagnostics and screening tool in type 2 diabetes.

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