

Increased serum interleukin-9 and interleukin-1 β are associated with depression in type 2 diabetes patients

Interleucina-9 e interleucina-1 β séricas aumentadas estão associadas à depressão em pacientes com diabetes tipo 2

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ABSTRACT

Background: Co-morbid diabetes and depression are prevalent chronic conditions negatively affecting quality of life (QoL). Inflammation has been considered as an integral mechanism in patients with both diabetes and depression. **Objective:** The aim of the present study was to investigate depression and its association with interleukins (IL)-1 β and IL-9 in type 2 diabetic patients (T2DM) and controls. The QoL in diabetic patient was also assessed. **Methods:** Eighty subjects were included, distributed among three groups: Group 1 - Healthy controls; Group 2 - T2DM patients without depression; Group 3 - T2DM patients with depression. Depression and QoL were assessed using Patient Health Questionnaire (PHQ-9) and The Audit of Diabetes-Dependent QoL (ADDQoL), respectively. IL-1 β and IL-9 were measured in serum samples of all the patients using ELISA kit. **Results:** The PHQ score in the Group 3 was significantly higher as compared to Group 1. The ADDQoL scores in the Group 3 were significantly higher as compared to Group 2. Levels of IL-9 and IL-1 β were elevated in Group 3, as compared to the other groups. **Conclusion:** This study showed positive association between depression and IL-1 β , IL-9 in T2DM patients. Additionally, the diabetic patients have poorer quality of life, which is further worsened by the presence of depression. Thus, routine assessment for the presence of depression is suggested in T2DM patients.

Keywords: Cytokines; Depression; Patient Health Questionnaire.

RESUMO

Introdução: O diabetes e a depressão comórbidas são condições crônicas prevalentes que afetam negativamente a qualidade de vida (QdV). A inflamação tem sido considerada como um mecanismo integral em pacientes com diabetes e depressão. **Objetivo:** Investigar a depressão e sua associação com interleucinas (IL)-1 β e IL-9 em pacientes diabéticos tipo 2 (DM2) e controles. A QdV em diabéticos também foi avaliada. **Métodos:** Foram incluídos 80 indivíduos, divididos em três grupos: Grupo 1 - controles saudáveis; Grupo 2 - pacientes com DM2 sem depressão; Grupo 3 - pacientes com DM2 com depressão. A depressão e a QdV foram avaliadas usando o Questionário de Saúde do Paciente (*Patient Health Questionnaire* — PHQ-9) e a auditoria de QdV dependente de diabetes (*Audit of Diabetes-Dependent Quality of Life* — ADDQoL), respectivamente. IL-1 β e IL-9 foram medidas em amostras de soro de todos os pacientes utilizando kit de ELISA. **Resultados:** O escore do PHQ no grupo 3 foi significativamente maior em comparação ao grupo 1. Os escores de ADDQoL no grupo 3 foram significativamente maiores em comparação ao grupo 2. Os níveis de IL-9 e IL-1 β foram elevados no grupo 3, como em comparação com os outros grupos. **Conclusão:** Este estudo mostrou associação positiva entre depressão e IL-1 β , IL-9 em pacientes com DM2. Além disso, os pacientes diabéticos têm pior QdV, o que é ainda piorado pela presença de depressão. Assim, a avaliação rotineira da presença de depressão é sugerida em pacientes com DM2.

Palavras-chave: Citocinas; Depressão; Questionário de Saúde do Paciente.

Diabetes Mellitus (DM) is a complex and heterogeneous chronic metabolic disease affecting 425 million people worldwide. It is estimated that the number of diabetic patients would increase to 700 million by 2045¹. Type 2 DM (T2DM), also called non-insulin-dependent or adult-onset diabetes, accounts for approximately 90% of all diabetes cases² and is

the seventh leading cause of death worldwide³. Depression is a common mental health disorder affecting more than 300 million people around the globe⁴. Various studies indicate that depression is more prevalent in adults with diabetes as compared to the general population⁵. The prevalence of depression among individuals living with diabetes has

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been estimated between 9 and 35%. A study reported a 43% increase in the risk of developing depression over six years for participants with baseline diabetes and a 102% risk for diabetes among those with depression at baseline⁶. The occurrence of clinically significant depression in patients with diabetes has been reported to be associated with biochemical changes either directly due to illness or hypoglycemic drug treatment⁷. Depression in diabetic patients has been found to be associated with insulin resistance, deranged circadian rhythms, and hypothalamic-pituitary-adrenal (HPA) axis⁸. Depression has also been linked with diabetes via biological and behavioral pathways such as neurohormonal pathways, alterations in glucose transport, and increased immunoinflammatory activation⁹. The co-occurrence of depression and T2DM is associated with increased morbidity, mortality, and health care costs, as well as decreased QoL and productivity¹⁰. Depression, when accompanied by macrovascular and microvascular complications, further worsen the QoL of the patient¹¹.

Inflammation has been ascertained as an integral mechanism in patients with both diabetes and depression. Certain clinical studies have reported that raised serum markers of inflammation, particularly IL-6, are associated with the onset of T2DM¹². Different cohort studies indicate the involvement of activated innate immunity in patients with T2DM¹¹. Depression has been found to be associated with impaired immune system and increased susceptibility to various diseases. An increase in plasma cytokines and acute phase protein concentration has been reported in the blood of depressed patients. Cytokines affect multiple CNS functions that are dysregulated during depression. Moreover, external administration of IL into the CNS has been found to induce immune function and produce stress-like effect on behavior¹³. Studies have highlighted higher levels of IL-1 β and IL-6 in patients with T2DM and depression¹⁴. IL-9, which is a Th2-related cytokine, has been reported to be over-expressed in the *post mortem* brains of depressed people¹⁵. It is a pleiotropic cytokine whose elevated levels have been linked to allergic lung inflammation¹⁶.

Despite the above probable mechanisms observed in depressive patients, it is not yet clear whether inflammation is associated with depression in diabetic patients. Thus, the aim of the present study was to investigate the depression in diabetic patients and its association with interleukins. We also assessed QoL in diabetic patient.

METHODS

Study site, duration, design, and population

This study was conducted in Hakeem Abdul Hameed Centenary Hospital, Jamia Hamdard, New Delhi, from March 2018 to May 2018 after approval was obtained from Ethics

committee. This case control study was conducted to investigate the association between depression and diabetes. The study focused on diabetic patients who attended diabetic clinic in the HAHC Hospital (Figure 1). Healthy human subjects, aged ≥ 18 years and ≤ 65 years, and able to give informed consent were included as controls. Patients diagnosed with T2DM, aged ≥ 18 years and ≤ 65 years, and ability to give informed consent were included as cases.

Cases with T1DM, severe psychiatric disorders (e.g.; alcohol abuse, severe depression, schizophrenia, bipolar disorder), already on psychotropic drug, severe complications of diabetes (i.e., amputation, blindness, renal insufficiency, and dialysis), liver disease, renal disease, primary hyperparathyroidism, cancer, HIV, obesity, congestive heart failure, myocardial infarction or coronary artery bypass surgery, or percutaneous coronary intervention within the previous 6 months, cardiac arrhythmias, and inability or unwillingness to give written informed consent were excluded.

Ethical considerations

This study was conducted in accordance with the guidelines of Declaration of Helsinki. Ethical approvals were obtained from the Ethics Committee of Hamdard Institute of Medical Sciences and Research (HIMSR), and the Institutional Ethics Committee of the School of Pharmaceutical Education and Research (SPER). Written informed consent was voluntarily obtained from all participants before their in the study.

Sampling method & sample size

The estimated sample size for this study was 80 participants. The calculation of the sample size was conducted on the assumptions that confidence level (95%), margin of error not more than (5%), and prevalence of depression among diabetes patients of (50%). The value of 95% confidence interval (95%CI) from the normal distribution is 1.96 and for practical reasons we rounded it to be 2. Participants were recruited in diabetic clinic in the HAHC Hospital. All type-2 diabetic patients visiting the diabetes clinic fulfilling the inclusion criteria and willing to participate were included in the study.

Data collection

Questionnaires

The data was collected by “face-to-face” interview using two standardized questionnaires: Patient Health Questionnaire-9 (PHQ 9) and The Audit of Diabetes-Dependent QoL (ADDQoL).

Assessment of depression

The PHQ-9 questionnaire was used for assessing depression among diabetic with depression and control patients. The PHQ-9 offers a categorical algorithm for the

diagnosis of depressive disorder. Major depression is diagnosed if five or more of the nine depressive symptoms criteria were present for at least “more than half the days” in the previous two weeks (suicidal thoughts count if present at all) and one of the symptoms is depressed mood or anhedonia. In addition, the sum score [0-27] were used for screening purposes and for measuring depression severity. The cut-off point that is most widely used to indicate a positive case for depressive disorder is the sum score of 10 or higher¹⁷.

Assessment of quality of life

The ADDQoL questionnaire was used for assessing QoL in cases. The ADDQoL is a 19-item questionnaire that measures the impact of diabetes on specific aspects of life and the importance of these aspects of life for QoL. Being an “individualized” measure, it is not assumed that all items are applicable to everyone: five items, including working life, have a preliminary ‘Yes/No’ option¹⁸.

Assessment of interleukins

Blood samples were collected on the day of their assessment of depression. The blood samples were processed, the samples were centrifuged, and the serum was stored at -80°C. Biomarkers of subclinical inflammation were measured in serum samples by using ELISA technique (Krishgen Biosystems Private Ltd., Mumbai, India).

Statistical analyses

Data were analyzed using IBM SPSS software (version 22.0) (IBM Corp., Armonk, NY, USA). Analyses were based on 80 individuals with controls and T2DM with a complete core data set comprising age, sex, body mass index (BMI), and duration of diabetes. Data are presented as SD or percentage (%) for continuous or categorical variables. Difference between controls and cases were tested using Student’s t-test (two sided) and Fisher’s exact test. Unadjusted correlations between biomarkers of subclinical inflammation and/or depression scores were estimated using unpaired t-test or nonparametric test (two sided) correlation and corresponding p-value. The $p < 0.05$ was considered statistically.

RESULTS

Baseline data

Eighty subjects were included in the study, distributed among three groups:

- Group 1: controls (healthy individuals).
- Group 2: T2DM patients without depression.
- Group 3: T2DM patients with depression.

The mean±SD age of Group 1, Group 2, and Group 3 was 45.0±8.1, 47.9±7.8, and 46.7±6.1 years, respectively.

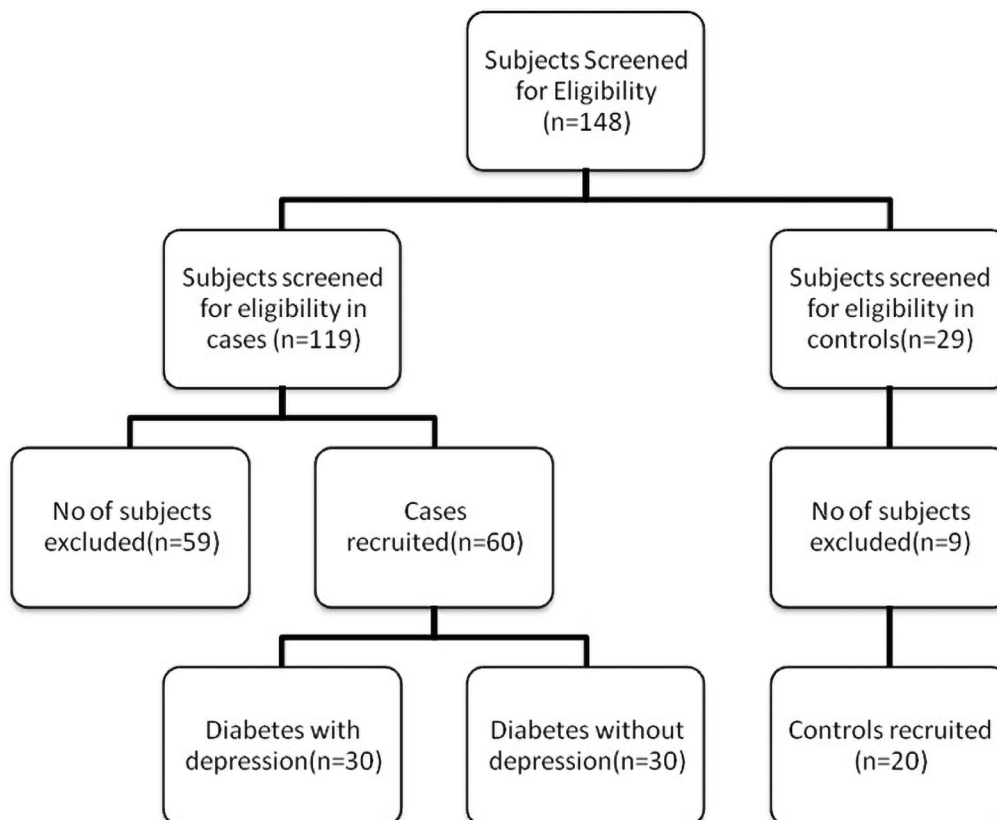


Figure 1. Study flow chart.

Group 2 and Group 3 had a known T2DM of mean duration 5.3±4.4 and 6.0±3.9 years, p=0.49.

There was no significant difference in mean age, gender distribution, RBS (random blood sugar), FPG (fasting plasma glucose), HbA1c, time spent on exercise between the three groups. The socio-demographic characteristics of study participants are shown in Table 1.

Assessment of depression

The PHQ-9 scores in Group 1 and Group 3 were 1.3±3.3 and 11.9±1.9 respectively (p<0.001). It was observed that the PHQ scores in the Group 3 were higher as compared to Group 1. There was a significant difference between both the groups. The PHQ-9 scores in Group 1 and Group 2 were 1.4±3.3 and 1.5±2.0 respectively (p=0.88).

Assessment of QoL by ADDQoL

The ADDQoL scores in Group 2 and Group 3 were 2.3±0.5 and 2.6±0.7 (p=0.04). There was a clear difference in the QoL scores for the Group 3 when compared with the Group 2. Between these two groups, Group 3 was significantly higher score compared to Group 2 (Figure 2).

Assessment of IL-1β in cases and controls

Levels of IL-1β were found to be significantly higher in Group 3 or Group 2 as compared to Group 1. Additionally, Group 3 had significantly higher IL-1β concentration as compared to Group 2 (Figure 3).

Assessment of IL-9 in cases and controls

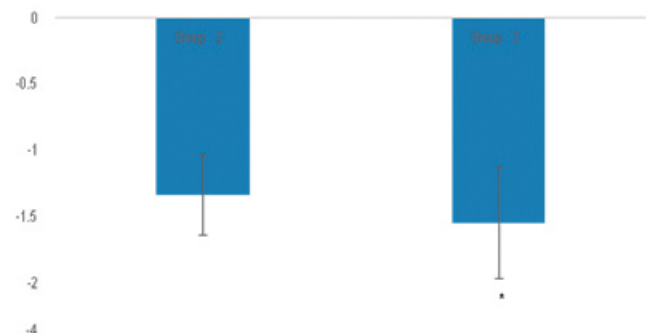
Levels of IL-9 were found to be significantly higher in Groups 2 or 3 as compared to Group 1. Additionally, Group 3 had significantly higher IL-9 concentration as compared to Group 2 (Figure 3).

Correlation between IL-9, IL-1β, and PHQ

A positive association was found between IL-9 and PHQ-9 (r=0.6191 and p=0.003), IL-1β and PHQ-9 (r=0.7783 and p=0.0001) in Group 3 (Figure 4).

Correlation between IL-9, IL-β, and ADDQoL

An inverse association was found between ADDQoL and IL-9 (r=-0.5737 and p=0.0009), ADDQoL and IL-1β (r=-0.5501 and p=0.0016) in Group 2 (Figure 5).



Group 2: T2DM patients without depression; Group 3: T2DM patients with depression. *p<0.05.

Figure 2. ADDQoL scores in Groups 2 and 3.

Table 1. Baseline characteristic of patients.

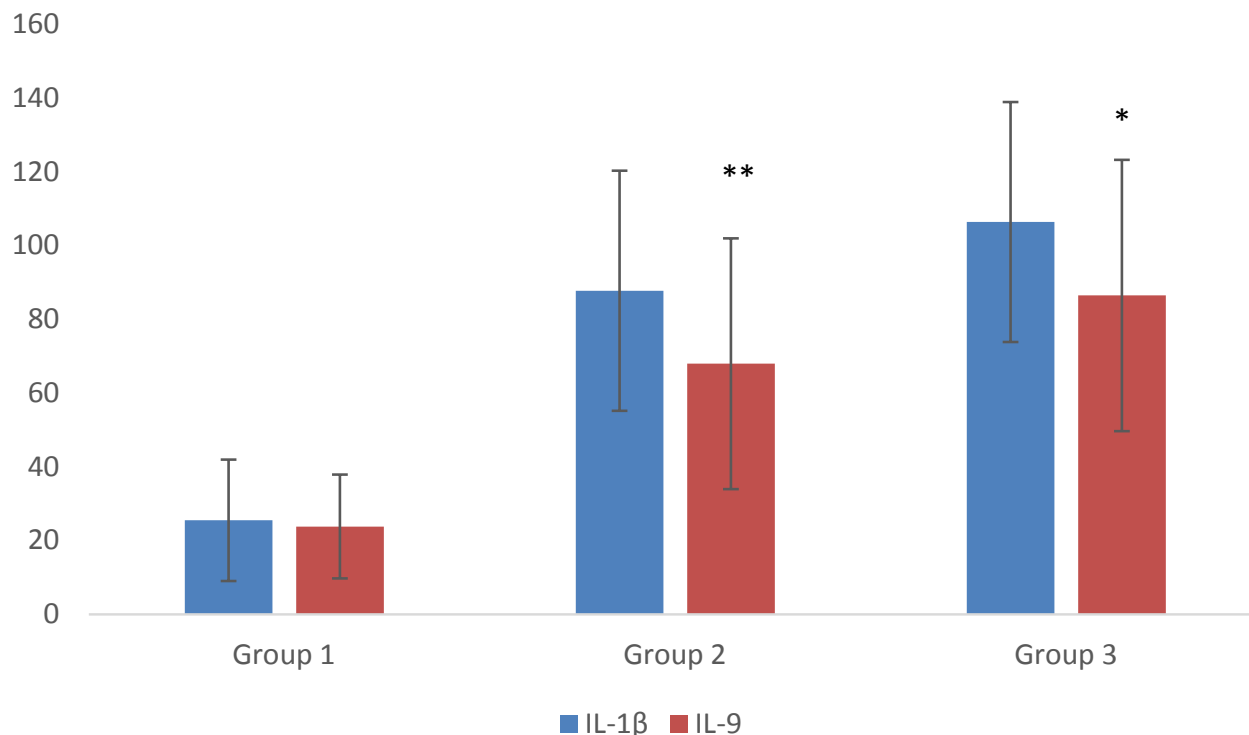
Characteristic	Group 1 (n=20)	Group 2 (n=30)	p-value	Group 1 (n=20)	Group 3 (n=30)	p-value	Group 2 (n=30)	Group 3 (n=30)	p-value
Age	45.0±8.1	47.9±7.8	0.18	45.0±8.1	46.7±6.1	0.58	47.9±7.5	46.7±6.1	0.31
Sex									
Female	6 (12%)	13 (26%)	0.38	6 (12%)	11 (22%)	0.76	13 (22%)	11 (18%)	0.79
Male	14 (28%)	17 (34%)		14 (28%)	19 (38%)		17 (28%)	19 (32%)	
BMI	24.3±2.5	24.8±3.8	0.99	24.3±2.5	25.0±3.5	0.43	24.8±3.8	25.0±3.5	0.82
Employment									
Working	13 (26%)	21 (42%)	0.76	13 (26%)	19 (38%)	1	21 (35%)	19 (32%)	0.78
Non-working	7 (14%)	9 (18%)		7 (14%)	11 (22%)		9 (15%)	11 (18%)	
Exercise	0.4±0.4	0.4±0.4	0.95	0.4±0.4	0.4±0.4	0.95	0.4±0.4	0.38±0.39	0.99
Diet									
Vegetarian	6 (12%)	6 (12%)	0.57	6 (12%)	8 (16%)	1	6 (10%)	8 (13%)	0.76
Non-veg	14 (28%)	24 (48%)		14 (28%)	22 (44%)		24 (40%)	22 (37%)	
Sun exposure	1.3±0.5	1.4±1.0	0.79	1.3±0.5	1.2±0.9	0.38	1.4±1.0	1.2±0.9	0.56
RBS							244.8±70.3	265.4±89.1	0.32
FPG							165.8±60.6	180.0±64.1	0.38
HbA1c duration of DM							8.4±1.7	8.6±2.3	0.61
							5.3±4.4	5.1±4.1	0.83

Group 1: controls healthy individual; Group 2: T2DM patients without depression; Group 3: T2DM patients with depression; BMI: body mass index; RBS: random blood sugar; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; T2DM: type 2 Diabetes Mellitus.

DISCUSSION

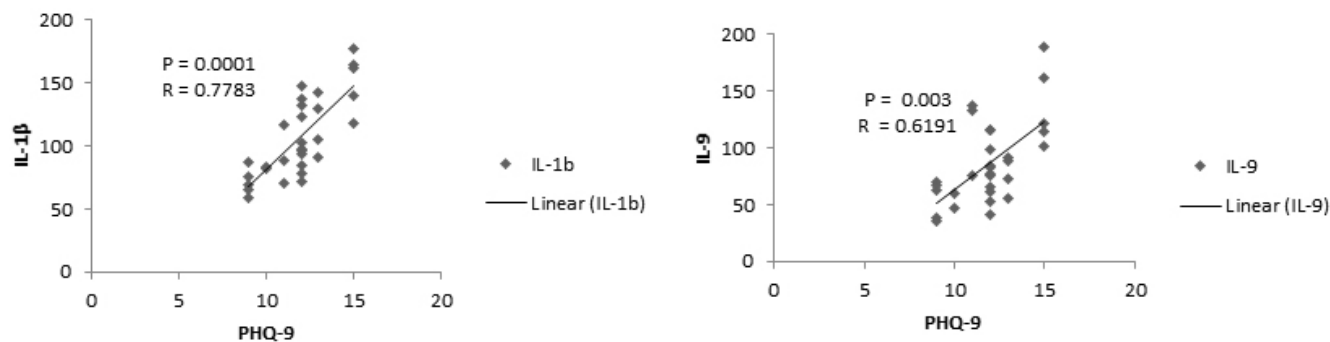
The current study was performed to assess the association of depression with IL-1 β and IL-9 in T2DM. The increased

susceptibility to depression in individuals with T2DM is yet to be clearly understood. Depression is linked with physiological changes in the neuroendocrine system. The hidden cause of depression is thought to be related to changes in the



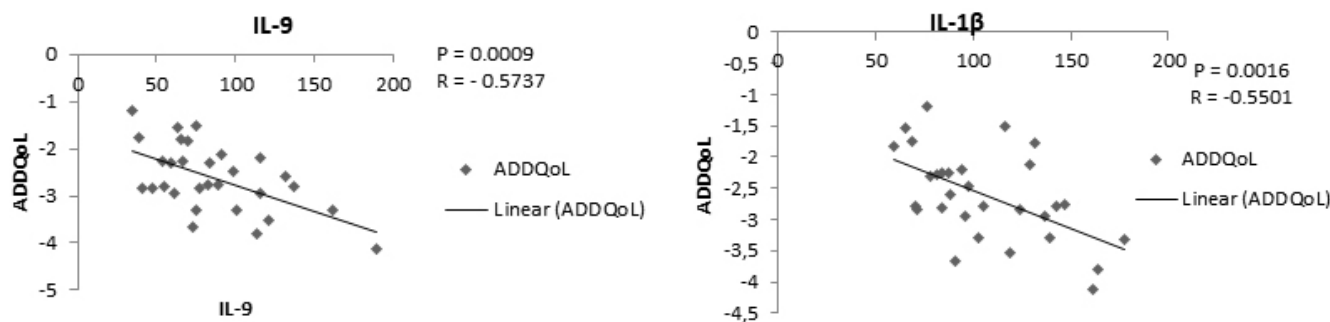
Group 1: Controls (healthy individuals); Group 2: T2DM patients without depression; Group 3: T2DM patients with depression; * $p < 0.05$; ** $p < 0.001$.

Figure 3. Levels of IL-1 β and IL-9 in the three groups.



Group 3: T2DM patients with depression.

Figure 4. Correlation between PHQ-9 scores with IL-9 and IL-1 β in Group 3.



Group 2: T2DM patients without depression.

Figure 5. Correlation between ADDQoL scores with IL-9 and IL-1 β in Group 2.

neurotransmitters in the brain such as serotonin (5-HT), dopamine (DA), and norepinephrine (NE), which are monoamine neurotransmitters that affect mood and behavior. Counter-regulatory hormones such as catecholamine, glucocorticoids, growth hormone, and glucagon are believed to be activated during psychological stress. The activation of the counter regulatory hormones interferes in the natural action of insulin, leading to insulin being unable to lower glucose and instead elevating blood glucose. The increase in glucose level creates a major challenge in maintaining metabolic control. Poor glycemic control and functional impairment due to increasing diabetes complication may cause or worsen depression¹⁹.

The results of our study showed that serum IL-1 β levels in T2DM patients were significantly higher than controls. Additionally, T2DM patients with depression had significantly higher serum IL-1 β levels than patients without depression. These findings are in agreement with several other clinical studies. A prospective population-based study showed a higher production capacity of the pro-inflammatory cytokine IL-1 β preceding a greater increase of depressive symptoms²⁰. Another prospective study showed increased levels of IL-1 β in T2DM as compared to the control subjects²¹. A previous clinical trial showed association between biomarkers (IL-1RA and IL-18) of subclinical inflammation and depressive symptoms in patients with T1DM and T2DM¹². A study showed higher levels of IL-1 β and IL-6 in patients with T2DM and depression¹⁴. Similar cross-sectional study in newly diagnosed T2DM patients demonstrated that higher depressive symptom scores were associated with higher concentration of IL-1 β and other inflammatory biomarker. The increases in concentration of the inflammatory markers were seen in the study suggesting the role of inflammation in the pathogenesis of depression¹¹.

The present study found significantly higher serum IL-9 levels in T2DM patients as compared to healthy controls. Moreover, patients with depression had significantly higher levels of serum IL-9 as compared to those without depression. IL-9 is a pleiotropic cytokine with anti-inflammatory effects. IL-9 has been associated with asthma, atherosclerosis, Hodgkin's disease, and cancer in humans²². However, to the best of our knowledge, there are only few studies available assessing IL-9 in the context of depression or anxiety symptoms. A

previous clinical study has observed that IL-9 cytokine correlated positively with prenatal depressive and overall anxiety symptoms¹⁶. Another study conducted on *post-mortem* brain tissues samples showed that IL-9 was over-expressed in the brains of depressed people¹⁵. Additionally, animal study conducted on mice has demonstrated IL-9 to be commonly reported cytokine in depressive like behaviors that were associated with local distinct neuroinflammation²³.

Depression is one of the most neglected symptoms in diabetic patients and is directly linked with lowering the QoL²⁴. The present study demonstrated significantly poorer QOL in diabetics with depression as compared to those without depression. Our finding is in line with previous literature. Cross-sectional studies have demonstrated a poor QoL in diabetic patients with depression as compared to patients without depression²⁵. A similar case-control study showed lower QOL in diabetics with depression as compared to patients without depression²⁶. Moreover, several cross-sectional studies have also demonstrated lower scores of QOL in diabetics²⁷.

Our study has several limitations that need to be mentioned. Some of the data, such as duration of T2DM, exercise, BMI and age were self-reported or were obtained from the patients' medical records. This could have led to recall bias. As this was a case-control study, no causal relationship can be inferred. Lastly, the sample size was small which might not represent all diabetic patients.

In conclusion, this study showed positive association between depression and IL-1 β , IL-9 in T2DM patients. Additionally, diabetic patients have poorer quality of life, which is further worsened by the presence of depression. The strength of the relationship between lifetime experience of depression and diabetes risk suggest that intervention designed to lessen the burden of diabetes should focus on depression that occurs at any time moment over a person's lifespan instead only that which is found immediately at the time of diabetes diagnosis or treatment.

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