Interplay of Systemic Inflammation and Uncontrolled Type-2 Diabetes Mellitus initiates Cognitive Dysfunction and Depression among Diabetic Patients

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Abstract

Background: Type-2 diabetes mellitus (T2DM) is associated with various chronic diseases, neurocognitive disorders, and vascular encephalopathy.

Objectives: screening of T2DM patients for the control of blood glucose (BG), the presence of manifestations of altered mood and/or cognitive impairment (CI), and dysregulated serum levels of tumor necrosis factor-α (TNF-α) and interleukin (IL)-6 and IL1β.

Patients and methods: 225 T2DM patients underwent estimation of fasting (FBG) and 2-h postprandial BG (PPBG), glycosylated hemoglobin A1c (HbA1c) and the homeostasis model assessment of insulin resistance (HOMA-IR) score. The presence and severity of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS). Mini-Mental State Examination (MMSE) and the Cognitive Change Index (CCI) were used to evaluate cognitive impairment (CI) and memory performance. Blood samples were obtained for ELISA estimation of serum cytokines' levels. Study outcome is the interrelation between the glycemic and psychological statuses and cytokines' levels.

Results: Sixteen and 56 patients showed manifest anxiety and depression, respectively while 155 patients had CI. Serum cytokines' levels showed positive correlation with PPBG, HOMA-IR and HbA1c%, and with HADS and CCI scores, while showing negative correlation with MMSE score. Regression analysis defined TNF-α as significant ($P<0.001$) predictor for high HADS-D and low MMSE scores ($P<0.001$), while PPBG levels were the significant ($P<0.001$) predictors for high HADS-A and high IL-1β ($P<0.001$) for high CCI.

Conclusion: Uncontrolled DM deleteriously impacted patients' psychological status, memory, and cognitive functions. High levels of serum TNF-α, PPBG, and HOMA-IR might predict impaired psychological status and memory function.

Keywords: Type-2 diabetes mellitus; Depression; Anxiety; Cognitive function; Memory function; Inflammatory cytokines; IL-6 and IL-1β.

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Introduction

Depression is a mental illness that may develop as a sequel to neuro-inflammation or due to changes in neuroplasticity in the prefrontal cortex and hippocampus **(Tung et al., 2023)**. Furthermore, depression was suggested to be associated with chronic systemic inflammation and a shift of the immune milieu in the inflammatory direction secondary to overproduction of proinflammatory cytokines **(Sin et al., 2023)**. and

Diabetes mellitus (DM) is increasing in worldwide prevalence, causes healthcare burden and is one of the most important underlying factors for all-cause mortality **(Arrieta-Canales et al., 2023)**. Type-2 diabetes mellitus (T2DM) is almost always associated with various chronic diseases, coronary artery disease **(Jian et al., 2023)** diabetic kidney disease **(Chen et al., 2024)**, peripheral sensory neuropathies **(Agyekum** and **Yeboah, 2023)** and micro- and macro-angiopathies **(Fukuda et al., 2023)**.

Depression is one of the most serious mental health comorbidities associated with DM, and its incidence in T2DM is double that of the general population **(Patil et al., 2023)**. Depressive symptoms and severe anxiety are independent increased risk of 1-year all-cause mortality in patients with T2D and screening for anxiety and depression is mandatory to identify patients at higher risk **(Shalaeva et al., 2024)**.Moreover, mood disorders, depression, and anxiety in T2DM patients are associated with poor outcomes **(Weiss et al., 2023)**.

The current study hypothesized that a disturbed inflammatory milieu may be the connecting stack between disturbed control of diabetes, the development of altered mood conditions, and cognitive impairment (CI) in T2DM patients. The study tries to screen a sample of T2DM patients for the extent of control of diabetes, the presence of manifestations of altered mood and/or CI, and a dysregulated inflammatory milieu to evaluate the frequency of diabetic patients who had anxiety, depression, memory dysfunction, and/or CI as primary outcome and to assess the interrelation between parameters evaluating the glycemic and psychological statuses and the estimated serum levels of inflammatory cytokines and to determine the predictability of estimated levels of glycemic control variates and inflammatory cytokines for the variates used to judge psychological functions.

Patients and Methods

All T2DM patients, either newly diagnosed or attending for follow-up underwent determination of demographic data including age, gender, body mass index (BMI), the presence of medical disorders, and history of previous intracranial surgical interventions and were evaluated for the presence of exclusion criteria. All patients were asked to attend the next morning fasting for at least 6-h to give the fasting blood samples.

Design: Multicenter prospective observational study

Setting : Departments of Psychiatry, Faculty of Medicine, Suez Canal University, and Internal Medicine, Faculty of Medicine, Zagazig University, in conjunction with multiple private centers.

Trial registration: The study protocol was approved by the departmental committee before case collections. The protocol was discussed freely with each patient, and those who accepted to participate in the study signed written, fully informed consent. After completion of case collection and obtaining the study outcomes, the final approval by the Local Ethical Committee was obtained with code: Research 5499#.

Sample size calculation: Previously, **Carr et al. (2021)** surveyed depression among diabetics and evaluated 106 patients suspected to have neuropsychiatric manifestations. Also, **Mone et al. (2022)** evaluated the CI in adults with diabetes through an evaluation of 179 patients. The null hypothesis of the current study is that the severity of depression and CI as judged by the HADS and MMSE scales were correlated with glycemic control status and levels of inflammatory cytokines. Using the G*Power (Version 3.1.9.2) **(Faul et al., 2007)**, the sample size that was calculated to provide a study power of 80% using α-error 5% and considering the effect size of 0.20 by the F test model defined 200 patients is the suitable number to ensure the certainty of the null hypothesis.

Inclusion criteria: T2DM patients who were free of exclusion criteria and accepted to sign the informed written consent to participate in the study were enrolled in the study. For comparative purposes, 30 healthy volunteers of cross-matched age, free of inclusion and exclusion criteria, were chosen from those attending the blood banks for blood donation and accepted to give blood samples as control for the measured serum cytokines' levels.

Exclusion criteria: T2DM patients who had previous cerebrovascular accidents, transient ischemic attacks, manifest peripheral ischemia, a history of diabetic ketoacidosis coma, Alzheimer, dementia, or severe peripheral neuropathy were excluded from the study.

Evaluation Tools

A) **BMI determination & grading**: BMI (kg/m^2) was calculated as weight (kg)/ height (m^2) **(Bray, 1992)** and was graded according to WHO guidelines as Av weight (BMI<24.9 kg/m^2), OV (BMI=25-<30 kg/m^2) and Ob women (BMI=30-<35 kg/m^2) and morbid Ob (BMI>35 kg/m^2) **(WHO, 1995)**.

B) **Psychiatric evaluations**

1. **The Hospital Anxiety and Depression Scale (HADS)**, which is a reliable instrument for detecting anxiety (HADS-A) and depression (HADS-D) in the outpatient clinics. HADS is a self-assessment questionnaire consisted of two domains to assess anxiety and depression symptoms, each domain consisted of 7 self-answered questions and answers were rated using 4-point Likert scale and score of ≤7 indicated normal function, 8-10 defined borderline abnormal case and score of ≥11 indicated abnormal case for either domain **(Zigmond and Snaith, 1983; Rishi et al., 2017)**.
2. **The Mini-Mental State Examination (MMSE)**, which is a validated 30-point questionnaire to assess cognitive function (CF), and scores were interpreted as normal CF (score = 25-30), mild CI if score was 20-25, moderate CI at score range of 10-20, and score of <10 indicates severe CI **(Folstein et al., 1975)**.
3. **The Cognitive Change Index (CCI)** is a self-answered 20-item questionnaire to rate the participant's CF compared to the previous five years. Twelve items are concerned with memory performance; five items evaluate the executive function and three items evaluate language. The response to each item was scored on 0-4 Likert scale, with 0 = no

change or normal ability, 1 = minimal change or slight/occasional problem, 2 = some change or mild problem and 3 = clearly noticeable change or moderate problem, 4 = much worse or severe problem. The sum of the scores of the 20 items gives the CCI self-report, which range between 0 and 80, with higher scores indicating greater decline **(Rattanabannakit et al., 2016).** The CCI cutoff value for significant cognitive complaints is set at >16/80 **(Risacher et al., 2015)**.

C) **Evaluation of the Glycemic Status**

1. **The 75-oral glucose tolerance test (75-OGTT)** to assure of the diagnosis of DM with fasting blood glucose (FBG) ≥92 mg/dl and 2-h postprandial blood glucose (2-h PPBG) ≥153 mg/dl indicated that the patient is diabetic.
2. **Assessment of insulin resistance** using the homeostasis model assessment of insulin resistance (HOMA-IR) score and score of ≥2 is indicated IR **(Matthews et al., 1985)**.
3. Control of diabetes through the preceding three months was ascertained according to the estimated level of glycosylated hemoglobin A1c (HbA1c) a 4-6% level indicates healthy blood glucose control; a HbA1c was in range of 6-6.5% indicates a prediabetic state with controlled blood glucose; a HbA1c in the range of 6.5-8% indicates that patient is diabetic but has good diabetic control; a HbA1c level >8% indicates that the patient is diabetic and requires interference to achieve control **(Gillett et al., 2009)**.

D) **Evaluation of inflammatory status**

Blood samples were obtained aseptically, allowed to clot, and centrifuged to obtain serum samples that were collected in clean, dry Eppendorf tubes to be frozen at -20^{o}C until being estimated for serum tumor necrosis factor-α (TNF-α; catalog no. ab181421, Abcam Inc., San Francisco, USA) **(Coughlan et al., 2001)**, interleukin-1β (IL-1β; catalog no. ab214025, Abcam Inc., San Francisco, USA) **(Xu et al., 2019)** and interleukin-6 (IL-6; catalog no. ab178013, Abcam Inc., San Francisco, USA) **(Das and Poole, 1993)** using the enzyme linked immunoassay (ELISA) kit by quantitative sandwich enzyme immunoassay technique.

Statistical analysis

The Kolmogorov-Smimov test of normality and the normal Q-Q plots were used to test the data normality. The data are presented as mean, standard deviation, numbers and percentages. The significance of difference in serum cytokines' levels estimated in patients and controls was assessed by One-way ANOVA test with Tukey HSD. Pearson's correlation analysis was used to assess the correlation between the estimated levels of glycemic control variates, serum cytokines' levels as independent variants, and the dependent variables, including the levels of the estimated psychological variates. Multivariate regression analysis was used to verify the correlated variates as predictors for scores of tools used for psychological assessments. The optimum cut-off point for significance was $P < 0.05$. Statistical analyses were performed using IBM® SPSS® Statistics software (Version 22, 2015; Armonk, USA).

Results

The preliminary evaluation excluded 21 patients; 7 patients had previous cerebrovascular accident, 5 patients had previous diabetic comas, 5 patients had deteriorated liver functions, two patients had previous carotid endartrectomy and two patients had peripheral vascular diseases. The study included 225 diabetic patients subjected to evaluation according to the study protocol. Most of the studied patients were older than 50 years (85.4%), females (58.2%) and obese (96.4%), and 22 patients (9.8%) had compensated medical problems (**Table.1**).

Table 1.Patients' enrolment data

Variables			**Findings**
Age (Years)	**<40**		3 (1.3%)
	40-49		30 (13.3%)
	50-59		85 (37.8%)
	≥60		107 (47.6%)
	Mean (±SD)		57.6±6.4
Gender	**Males**		94 (41.8%)
	Females		131 (58.2%)
Compensated medical problems	**No**		203 (90.2%)
	Yes	**Cardiac**	7 (3.1%)
		Renal	5 (2.2%)
		Vascular	4 (1.8%)
		Hepatic	6 (2.7%)
Body mass index (kg/m2)	**Overweight**		8 (3.6%)
	Obese-I		47 (20.9%)
	Obese-II		138 (61.3%)
	Obese-III		32 (14.2%)
	Mean (±SD)		33.1±3.4

All patients had psychological upset, but depression was the most prevalent where only 60 patients (26.7%) showed HADS-D at or less than the diagnostic cutoff point for the presence of depression (HADS-D ≤7), while 165 patients (73.3%) showed manifestations of depression; 109 patients (48.4%) showed HADS-D of <11 and 56 patients (24.9%) showed HADS-D of ≥11 which is indicative of definite depression with mean value of HADS-D of 9.12±2.38. Regarding anxiety, evaluation of HADS-A scorings excluded anxiety in 97 patients (43.1%) who showed a HADS-A score of ≤7, while 112 patients (49.7%) were borderline anxiety patients with HADS-A score <11 and only 16 patients (7.2%) had HADS-A score of ≥11 that indicated manifest anxiety with mean value of HADS-A of 7.94±1.85.

According to MMSE scorings, 70 patients (31.1%) had MMSE score within the normal range and were considered as cognitively normal patients, while the remaining 155 patients showed varied degrees of CI with 84 patients (37.3%) had mild, 56 patients (24.9%) had moderate and 15 patients (6.7%) had severe CI with mean value of MMSE of 21.3±5.7. Moreover, 147 patients (65.3%) showed no change in their CF with CCI of ≤16, while 78 patients (34.7%) showed CCI of >16 that pointed to change in their cognitive function within the last years with mean value of CCI of 19.8±12.35 (**Table.2**).

Table 2: Psychological evaluation of the studied patients

Data				Findings
Hospital Anxiety and Depression Scale (HADS)	Depression	Score		9.12±2.38
		Frequency	Normal (≤7)	60 (26.7%)
			Borderline abnormal (8-10)	109 (48.4%)
			Abnormal (≥11)	56 (24.9%)
	Anxiety	Score		7.94±1.85
		Frequency	Normal (≤7)	97 (43.1%)
			Borderline abnormal (8-10)	112 (49.7%)
			Abnormal (≥11)	16 (7.2%)
The Mini-Mental State Examination (MMSE)		Score		21.3±5.7
		Frequency	Normal (25-30)	70 (31.1%)
			Mild (20-24)	84 (37.3%)
			Moderate (10-20)	56 (24.9%)
			Sever (<10)	15 (6.7%)
The Cognitive Change Index (CCI)		Score		19.8±12.35
		Frequency	Normal (≤16)	147 (65.3%)
			Abnormal (>16)	78 (34.7%)

The estimated blood glucose levels assured the presence of DM with mean FBG of 156.8±9.2; range: 128-176 mg/dl and mean 2-h PPBG of 237±29.4; range: 167-276 mg/dl. Only 13 patients (5.8%) had 2-PPBG <180 mg/dl, while 212 patients (94.2%) had 2-h PPBG >180 mg/dl with definite glycosuria.

According to estimated HbA1c levels, 36 patients (16%) showed strict glycemic control, 129 patients (57.3%) had controlled diabetes and 60 patients (26.7%) showed uncontrolled diabetes. Proper control of diabetes resulted in improved insulin resistance in 65 patients (28.9%), while 160 patients (71.1%) were still insulin resistant (**Table.3**).

Table 3. Results of evaluations of blood glucose control

Data				Findings
The 75-oral glucose tolerance test (OGTT)	FBG (mg/dl)			156.8±9.2 (128-176)
	1-h PPBG (mg/ml)			309.6±39.2 (239-390)
	2-h PPBG (mg/dl)			237±29.4 (167-276)
The homeostasis model assessment of insulin resistance (HOMA-IR)	Fasting plasma insulin (µIU/L)			8.64±1.94 (5.5-16.8)
	HOMA-IR score			2.38±0.56 (1.46-4.27)
	Frequency	Insulin resistant		160 (71.1%)
		Insulin sensitive		65 (28.9%)
Glycosylated hemoglobin A1c (HbA1c)	Estimated HbA1c level (%)			7.46±1 (6.1-11.7)
	Control of diabetes	Controlled	6-6.4%	36 (16%)
			6.5-8%	129 (57.3%)
		Uncontrolled	>8%	60 (26.7%)

The Estimated serum cytokines' levels were significantly (P<0.001) higher in patients' samples than in control samples (**Table.4**).

Table 4. Serum levels of the studied cytokines in patients' versus controls' samples

Variables	Controls (n=30)	Patients (n=225)	P-value
TNFα (pg/ml)	12.25±2.36	23.3±9.3	<0.001
IL-6 (pg/ml)	11.92±3.85	32±14.3	<0.001
IL-1β (pg/ml)	2.66±1.2	29.3±9.5	<0.001

The estimated 2-h PPBG and HbA1c% showed positive significant correlation with the estimated serum levels of TNFα and IL-1β, while HOMA-IR score showed positive significant correlation with serum levels of TNFα and IL-6 (**Table.5**).

Table 5. Correlation analysis of the relation between the estimated cytokines' levels and the determined markers of control of diabetes **and psychological scores**

Variables	TNFα		IL-1β		IL-6	
	"r"	P	"r"	P	"r"	P
2-h PPBG	0.233	<0.001	0.444	<0.001	0.103	0.124
HOMA-IR score	0.168	0.011	0.094	0.160	0.229	0.001
HbA1c%	0.259	<0.001	0.148	0.026	0.228	0.228

The determined HADS scores and CCI showed positive significant correlation, while MMSE scores showed negative significant correlation with the estimated 2-h PPBG, HOMA-IR score and serum levels of TNFα and IL-1β. The determined HADS-D and CCI scores showed positive significant correlation, while MMSE scores showed negative significant correlation with serum levels of IL-6. Moreover, CCI scores were positively correlated while MMSE scores were negatively correlated with the estimated HbA1c% (**Table.6).**

Table 6. Correlation analysis of the relation between the determined psychological scores and scores of control of diabetes and the estimated cytokines' levels

Variables	HADS-D		HADS-A		MMSE		CCI	
	"r"	P	"r"	P	"r"	P	"r"	P
2-h PPBG	0.195	0.003	0.262	<0.001	-0.195	0.003	0.212	0.001
HOMA-IR score	0.221	0.001	0.204	0.002	-0.205	0.002	0.232	<0.001
HbA1c%	0.095	0.154	0.113	0.090	-0.191	0.004	0.137	0.040
TNFα	0.331	<0.001	0.189	0.004	-- 0.339	<0.001	0.241	<0.001
IL-1β	0.203	0.002	0.232	<0.001	-0.254	<0.001	0.315	<0.001
IL-6	0.231	<0.001	0.095	0.154	-0.195	0.003	0.227	0.001

Multivariate Regression analysis defined high serum TNF-α serum levels as the persistently significant predictor for high HADS-D and low MMSE scores, while high PPBG was the persistently significant predictor for high HADS-A score and high serum levels of IL-1β as the significant predictor for high CCI (**Table.7**).

Table 7. Regression analysis of the estimated PPBG and serum inflammatory cytokines as predictors for disturbed mood and CF as judged by HADS, MMSE and CCI scores

Model no.	HADS-D			HADS-A		
	Variables	B	P	Variates	β	P
1	TNF-α	0.331	<0.001	PPBG	0.262	<0.001
2	TNF-α	0.340	<0.001	PPBG	0.270	<0.001
	PPBG	0.209	0.001	TNF-α	0.201	0.002
3	TNF-α	0.289	<0.001	PPBG	0.221	0.001
	PPBG	0.234	<0.001	TNF-α	0.192	0.003
	IL-6	0.183	0.005	IL-1β	0.154	0.021
Model no.	**MMSE**			**CCI**		
	Variables	**B**	**P**	**Variates**	**β**	**P**
1	TNF-α	-0.339	<0.001	IL-1β	0.315	<0.001
2	TNF-α	-0.329	<0.001	IL-1β	0.305	<0.001
	IL-1β	-0.240	<0.001	TNF-α	0.228	<0.001
3	TNF-α	-0.337	<0.001	IL-1β	0.260	<0.001
	IL-1β	-0.193	0.003	TNF-α	0.236	<0.001
	PPBG	-0.148	0.021	PPBG	0.139	0.033

Discussion

Statistical analyses showed significant positive correlations between the estimated serum levels of inflammatory cytokines and measures of control of diabetes. Similarly, **Gohari et al. (2023)** found levels of IL-6 are significantly reduced with the use of sodium-glucose co-transporter-2 inhibitors, and assured the prognostic value of HbA1c levels to assess these reductions, and documented the positive association between IL-6 and the pathophysiology of metabolic-related disorders. These findings suggest a reciprocal relation between uncontrolled diabetes and a shift of body immune equilibrium towards the inflammatory side. In line with this assumption, **Mzimela et al. (2024)** reported that prediabetic state is associated with immune activation and significant increase in serum TNFα, CD40L, and fibrinogen concentrations, and T2DM patients showed increased levels of similar markers in addition to increases in serum C-reactive protein (CRP) and IL-6 than in normoglycemic subjects.

Multiple studies have suggested adipose tissue as the source of inflammatory cytokines in T2DM patients (**Ghozhdi et al., 2021; Kang and Lee, 2021; Dong et al., 2022; Makarewicz et al., 2022**), however, a recent experimental study detected the ability of alpha-ketoglutarate, a Krebs cycle intermediate metabolite, to suppress phosphorylated-Akt via augmentation of prolyl hydroxylase-2, leading to inhibition of platelet and leukocyte activation with subsequent inhibition of the release of pro-inflammatory cytokines **Agarwal et al. (2023)**. Another study suggested that hyperglycemia induces overexpression

of the allograft inflammatory factor-1, which promotes translocation of NF-κB p65 from the cytoplasm into the nucleus ending in a simulation of the NF-κB pathway with subsequent induction of IL-6 and TNF-α production **Wu et al. (2024)**. The results of these recent experimental works indicated a relation between disturbed glucose metabolism and the pathways and cellular components governing the synthesis and release of inflammatory cytokines.

On the other side, statistical analyses showed positive significant correlations between disturbed measures of control of diabetes, especially PPBG levels and high cytokines' levels, and both HADS-A, HADS-D, and CCI, with significant negative correlation with MMSE. These findings assured the certainty of the study null hypothesis and indicated that both DM and the inflammatory milieu seriously impacted the psychological, cognitive, and memory status of T2DM patients.

In line with this composite relation, recent systemic reviews detected significant negative correlation between IL-6, TNF-α, and CRP levels with cognitive function scorings **(Du et al. 2023),** insulin resistance leads to progressive loss of neurons and aggregation of the amyloid β and deposition of misfolded proteins in the brain's hippocampal and cortical neuronal regions **(Birajdar et al. 2023)** and a significant relation between high neutrophil/lymphocyte ratio and increased severity of CI **(Hung et al. (2023)**.

Moreover, **Abi Saleh et al. (2022)** prospectively found diabetes and inflammation might explain the relation between obesity and CI, **Saraya et al. (2023)** detected a positive correlation between serum proinsulin and worse cognitive scores, and attributed this to reduced brain insulin levels secondary to peripheral insulin resistance induced by high proinsulin levels and **Sánchez-Ortí et al. (2023)** documented that the combination of IL-6, TNF-α and apolipoproteins might act as discriminators between patients with different degrees of memory impairment. Moreover, **Zhang et al. (2023)** detected lower IL-10 in the plasma of T2DM patients with mild CI than those without CI and considered deregulated levels of IL-10 are risk factors for CI in T2DM patients. Also, **Okamoto et al. (2023)** reported significantly higher TNF-α levels in patients with comorbid major depressive disorder and T2DM than patients free of DM. Additionally, **Gao et al. (2024)** defined TNF-α and CRP levels to be significantly associated with the presence and severity of CI.

Moreover, recent studies assured that this interlacing relation between inflammatory cytokines and psychological disorders is not limited to diabetic patients, where **Klaus et al. (2021)** detected higher plasma levels of TNFα in schizophrenia patients than healthy controls, **Almulla et al. (2023)** reported that in first-episode major depressive disorder patients increased neurotoxicity is mainly driven by IL-16, TNF-α and IL-6, and scorings for depression, anxiety, and suicidal behavior scores were negatively associated with IL-1 receptor antagonist and **Shi et al. (2023)** detected anxiety, depression, and CI in 32.6, 39.4, and 19.4%, respectively of acute ischemic stroke patients and found high TNF-α and IL-6 levels were significantly correlated with higher anxiety rate, while high levels of TNF-α were positively correlated with increased depression rate and high IL-1β levels were positively and significantly associated with elevated CI rate.

Conclusion

High BG measures deleteriously impacted the psychological status, memory and cognitive function of T2DM patients, and high serum levels of inflammatory cytokines are the pivot axis for this relation. High levels of serum TNF-α, 2-h PPBG, and HOMA-IR might predict impaired psychological status and memory function. High serum levels of TNF-α might predict CI and poor control of blood glucose.

Limitation

Estimation of serum levels of anti-inflammatory cytokines was mandatory to assess the equilibrium of the immune milieu was the limitation of this study.

Recommendations

Further wide-scale multicenter studies are required to establish this interplay. Assessment of the role of the inflammatory adipocytokines in impairment of memory and cognitive functions was essential to documenting the role of inflammation as the focal point for the relation between T2DM and these impairments. Similar studies including T1DM patients are also essential to defining the role of insulin in the pathogenesis of memory and cognitive function.

References

- **Abi Saleh R, Lirette S, Benjamin E, Fornage M, Turner S, Hammond P, et al. (2022).** Mediation effects of diabetes and inflammation on the relationship of obesity to cognitive impairment in African Americans. Journal of the American Geriatrics Society, 70(10):3021-3029.
- **Agarwal S, Ghosh R, Verma G, Khadgawat R, Guchhait P. (2023).** Alpha-ketoglutarate supplementation reduces inflammation and thrombosis in type 2 diabetes by suppressing leukocyte and platelet activation. Clinical and Experimental Immunology; 214(2):197-208.
- **Agyekum JA, Yeboah K. (2023).** Peripheral sensory neuropathy is associated with circulating angiopoietins in type 2 diabetes patients in Ghana. Journal of Clinical and Translational Endocrinology, 34:100327.
- **Almulla A, Abo Algon A, Tunvirachaisakul C, Al-Hakeim H, Maes M. (2023).** T helper-1 activation via interleukin-16 is a key phenomenon in the acute phase of severe, first-episode major depressive disorder and suicidal behaviors. Journal of Advanced Research, S2090-1232(23)00349-1.
- **Arrieta-Canales M, Mukherjee J, Gilbert H, Flores H, Muñoz M, Aranda Z, et al. (2023).** Transforming care for patients living with diabetes in rural Mexico: a qualitative study of patient and provider experiences and perceptions of shared medical appointments. Global Health Action, 16(1):2215004.
- **Birajdar S, Mazahir F, Alam M, Kumar A, Yadav A. (2023).** Repurposing and clinical attributes of antidiabetic drugs for the treatment of neurodegenerative disorders. European Journal of Pharmacology, 961:176117.
- Bray GA. (1992). Pathophysiology of obesity. The American Journal of Clinical Nutrition, 55: 488S-94S.
- **Carr AL, Sluiman AJ, Grecian SM, Forster R, McLachlan S, Strachan MWJ, et al. (2021).** Depression as a risk factor for dementia in older people with type 2 diabetes and the mediating

effect of inflammation. Diabetologia, 64(2):448-457.

- **Chen Y, Kanwar Y, Chen X, Zhan M. (2024).** Aging and Diabetic Kidney Disease: Emerging Pathogenetic Mechanisms and Clinical Implications. Current Medicinal Chemistry, 31(6):697-725.
- **Coughlan MT, Oliva K, Georgiou HM, Permezel JMH, Rice GE. (2001).** Glucose-induced release of tumor necrosis factor-alpha from human placental and adipose tissues in gestational diabetes mellitus. Diabetic Medicine, 18:921–7.
- **Dong J, Wu B, Tian W. (2022).** Adipose tissue-derived small extracellular vesicles modulate macrophages to improve the homing of adipocyte precursors and endothelial cells in adipose tissue regeneration. Frontiers in Cell and Developmental Biology, 10:1075233.
- **Du Y, Zhang Q, Zhang X, Song Y, Zheng J, An Y, et al. (2023).** Correlation between inflammatory biomarkers, cognitive function and glycemic and lipid profiles in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Clinical Biochemistry, 121-122:110683.
- **Faul F, Erdfelder E, Lang AG, Buchner A. (2007).** G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods, 39:175-191.
- **Folstein MF, Folstein SE, McHugh PR. (1975).** "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." Journal of Psychiatric Research, 12:189-198
- **Fukuda S, Hagiwara S, Okochi H, Ishiura N, Nishibe T, Yakabe R, et al. (2023).** Autologous angiogenic therapy with cultured mesenchymal stromal cells in platelet-rich plasma for critical limb ischemia. Regen Therapy, 24:472-478.
- **Gaines-Das RE, Poole S. (1993).** The international standard for interleukin-6—evaluation in an international collaborative study. Journal of Immunological Methods, 160:147–53.
- **Gao J, Fan H, Wang X, Cheng Y, Hao J, Han S, et al. (2024).** Association between serum omega-3 PUFAs levels and cognitive impairment in never medically treated first-episode patients with geriatric depression: A cross-sectional study. Journal of Affective Disorders, 346:1-6.
- **Ghozhdi HD, Heidarianpour A, Keshvari M, Tavassoli H. (2021).** Exercise training and de-training effects on serum leptin and TNF-α in high fat induced diabetic rats. Diabetology & Metabolic Syndrome, 13(1):57.
- **Gillett MJ. (2009).** International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care, 32:1327–34.
- **Gohari S, Ismail-Beigi F, Mahjani M, Ghobadi S, Jafari A, Ahangar H, et al. (2023).** The effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on blood interleukin-6 concentration: a systematic review and meta-analysis of randomized controlled trials. BMC Endocrine Disorders, 23(1):257.

- **Hung K, Liu C, Wu J, Ho C, Lin M, Hsing C, et al. (2023).** Association between the neutrophil-to-lymphocyte ratio and cognitive impairment: a meta-analysis of observational studies. Frontiers in Endocrinology (Lausanne), 14:1265637.
- **Jian Z, Yao G, Guo H, Liu H, Li B, Yu B, et al. (2023).** The impact of baseline calcified plaque volume on coronary rapid plaque progression by serial coronary computed tomography angiography in patients with type 2 diabetes. Annals of Medicine, 55(1):2196438.
- **Kang X, Wang D, Zhang L, Huang T, Liu S, Feng X, et al. (2023).** Exendin-4 ameliorates tau hyperphosphorylation and cognitive impairment in type 2 diabetes through acting on Wnt/β-catenin/NeuroD1 pathway. Molecular Medicine, 29(1):118.
- **Klaus F, Mitchell K, Liou S, Eyler L, Nguyen T. (2021).** Chemokine MCP1 is associated with cognitive flexibility in schizophrenia: A preliminary analysis. Journal of Psychiatric Research, 138:139-145.
- **Luo H, Huang Y, Zhang Q, Yu, Xie Y, Meng X, et al. (2023).** Impacts of physical activity and particulate air pollution on the onset, progression and mortality for the comorbidity of type 2 diabetes and mood disorders. Science of The Total Environment, 890:164315.
- **Makarewicz A, Jamka M, Geltz J, Śmidowicz A, Kokot M, Kaczmarek N, et al. (2022).** Comparison of the Effect of Endurance, Strength, and Endurance-Strength Training on Inflammatory Markers and Adipokines Levels in Overweight and Obese Adults: Systematic Review and Meta-Analysis of Randomised Trials. Healthcare (Basel), 10(6):1098.
- **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. (1985).** Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 28:412–19.
- **Mone P, Gambardella J, Lombardi A, Pansini A, De Gennaro S, Leo AL, et al. (2022).** Correlation of physical and cognitive impairment in diabetic and hypertensive frail older adults. Cardiovascular Diabetology, 21(1):10.
- **Mzimela N, Sosibo A, Ngubane P, Khathi A. (2024).** Investigation into changes in inflammatory and immune cell markers in pre-diabetic patients from Durban, South Africa. Journal of Immunotoxicology, 21(1):2290282.
- **Okamoto N, Hoshikawa T, Honma Y, Chibaatar E, Ikenouchi A, Harada M, et al. (2023).** Effect modification of tumor necrosis factor-α on the kynurenine and serotonin pathways in major depressive disorder on type 2 diabetes mellitus. European Archives of Psychiatry and Clinical Neuroscience, 2023 Nov 22.
- **Patil R, Aswar U, Vyas N. (2023).** Pterostilbene ameliorates type-2 diabetes mellitus - Induced depressive-like behavior by mitigating insulin resistance, inflammation and ameliorating HPA axis dysfunction in rat

brain. Brain Research, 1817:148494.

- **Rattanabannakit C, Risacher SL, Gao S, Lane KA, Brown SA, McDonald BC, et al. (2016).** The cognitive change index as a measure of self and informant perception of cognitive decline: relation to neuropsychological tests. Journal of Alzheimer's Disease, 51:1145–55.
- **Risacher SL, Kim S, Nho K, Foroud T, Shen L, Petersen RC, et al. (2015).** APOE effect on Alzheimer's disease biomarkers in older adults with significant memory concern. Alzheimer's & Dementia. 2015, 11:1417–29.
- **Rishi P, Rishi E, Maitray A, Agarwal A, Nair S, Gopalakrishnan S. (2017).** Hospital anxiety and depression s cale assessment of 100 patients before and after using low vision care: A prospective study in a tertiary eye-care setting. Indian Journal of Ophthalmology, 65(11):1203-1208.
- **Sánchez-Ortí J, Correa-Ghisays P, Balanzá-Martínez V, Selva-Vera G, Vila-Francés J, Magdalena-Benedito R, et al. (2023).** Inflammation and lipid metabolism as potential biomarkers of memory impairment across type 2 diabetes mellitus and severe mental disorders. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 127:110817.
- **Saraya A, Tunvirachaisakul C, Sonpee C, Katasrila P, Sathaporn T, Tepmongkol S, et al. (2023).** Serum proinsulin levels as peripheral blood biomarkers in patients with cognitive impairment. Scientific Reports, 13(1):22436.
- **Shalaeva E, Bano A, Kasimov U, Atakov S, Mirakhmedova K, Dadabaeva N, et al. (2024).** Depression and anxiety symptoms are underestimated risk factors for postoperative prognosis in patients with Type 2 diabetes and peripheral artery disease undergoing partial foot amputation: Results from a prospective cohort study. Journal of Psychosomatic Research, 183:111824.
- **Shi Q, Li R, Qu Z, Lang Y, Sheng G, Ning J, et al. (2023).** Longitudinal change of six common inflammatory cytokines and their relationship to anxiety, depression, and cognitive impairment in acute ischemic stroke patients. Brazilian Journal of Medical and Biological Research, 56:e13025.
- **Sin R, Sotogaku N, Ohnishi Y, Shuto T, Kuroiwa M, Kawahara Y, et al. (2023).** Inhibition of STAT-mediated cytokine responses to chemically-induced colitis prevents inflammation-associated neurobehavioral impairments. Brain, Behavior, and Immunity, 114:173-186.
- **Tung T, Lai W, Lee H, Su K, Panunggal B, Huang S. (2023).** Attenuation of Chronic Stress-Induced Depressive-like Symptoms by Fish Oil via Alleviating Neuroinflammation and Impaired Tryptophan Metabolism in Aging Rats. Journal of Agricultural and Food Chemistry, 71(40):14550-14561.
- **Weiss F, Brancati G, Elefante C, Petrucci A, Gemmellaro T, Lattanzi L, et al. (2023).** Type 2 diabetes mellitus is associated with manic morbidity

in elderly patients with mood disorders. International Clinical Psychopharmacology.

- **WHO. (1995).** Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series 854. Geneva: World Health Organization.
- **Wu Q, Qin B, Wu X, Zhang M, Gan Z, Lan Y, et al. (2024).** Allograft inflammatory factor-1 enhances inflammation and oxidative stress via the NF-κB pathway of bladder urothelium in diabetic rat model. Cytokine, 173:156438.
- **Xu H, Shi Q, Mo Y, Wu L, Gu J, Xu Y. (2019).** Downregulation of α7 nicotinic acetylcholine receptors in peripheral blood monocytes is associated with enhanced inflammation in preeclampsia. BMC Pregnancy and Childbirth, 19(1):188.
- **Zhang H, Yang S, Zhu W, Niu T, Wang J, Yang M, et al. (2023).** Exosomal miR-let-7c-5p is involved in the cognitive function of type 2 diabetes mellitus patients by interleukin 10: A cross-sectional study. Journal of Diabetes, 15(11):978-986.
- **Zigmond AS, Snaith RP. (1983).** The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica, 67: 361–370.