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Original Research Article

The Role of Oxidative Stress and Inflammatory Markers in Cognitive Dysfunction in Diabetes Mellitus

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Abstract

Background: Cognitive decline is a significant complication observed in patients with diabetes mellitus, with increasing evidence pointing to the role of chronic systemic inflammation as a mediating factor. Elevated levels of inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been implicated in both diabetes-related metabolic dysfunction and neurodegenerative processes. This study aims to evaluate the association between inflammatory markers and cognitive decline in individuals with type 2 diabetes mellitus (T2DM).

Objective: To assess the prevalence of cognitive impairment among individuals with T2DM and investigate its relationship with inflammatory markers such as IL-6, TNF-α, and CRP.

Methods: A cross-sectional study was conducted at MGM Hospital, Warangal, Telangana, India, over a one-year period from January 2023 to December 2023. A total of 500 participants aged 50 years and above were enrolled, including 350 patients with T2DM and 150 non-diabetic controls. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Blood samples were collected to measure levels of IL-6, TNF-α, and CRP using enzyme-linked immunosorbent assay (ELISA). Anthropometric and clinical data, including HbA1c, fasting glucose, and lipid profiles, were also recorded. Statistical analysis included logistic regression to identify predictors of cognitive decline and correlation analysis to assess the relationship between inflammatory markers and cognitive scores.

Results: The prevalence of cognitive decline was significantly higher in the diabetic group (48%) compared to non-diabetic controls (18%, $p < 0.001$). Among the diabetic group, elevated levels of IL-6 (mean ± SD: 8.5 ± 3.2 pg/mL), TNF-α (12.1 ± 4.5 pg/mL), and CRP (6.8 ± 2.3 mg/L) were observed compared to controls (IL-6: 4.2 ± 1.8 pg/mL; TNF-α: 6.3 ± 2.7 pg/mL; CRP: 3.1 ± 1.4 mg/L, all $p < 0.001$). Cognitive decline in T2DM patients was significantly associated with higher IL-6 (OR: 2.45, 95% CI: 1.73–3.47, $p < 0.001$), TNF-α (OR: 2.18, 95% CI: 1.54–3.10, $p < 0.001$), and CRP (OR: 1.92, 95% CI: 1.39–2.66, $p < 0.001$). HbA1c levels were also significantly higher in participants with cognitive decline (8.6 ± 1.2%) compared to those without (7.4 ± 0.9%, $p < 0.001$). Correlation analysis showed a strong negative association between inflammatory marker levels and cognitive scores (IL-6: $r = -0.42$, $p < 0.001$; TNF-α: $r = -0.39$, $p < 0.001$; CRP: $r = -0.35$, $p < 0.001$). Additionally, dyslipidemia and longer diabetes duration (>10 years) were found to exacerbate cognitive impairment.

Conclusion: This study highlights a significant association between elevated inflammatory markers and cognitive decline in patients with T2DM. The findings emphasize the importance of monitoring inflammatory markers in diabetic individuals as potential predictors of cognitive impairment. Future research should explore targeted anti-inflammatory interventions to mitigate cognitive decline in this population.

Keywords: Cognitive decline, diabetes mellitus, inflammatory markers, IL-6, TNF-α, CRP, MMSE, MoCA, neuroinflammation.

Introduction

Cognitive decline is a growing public health concern, particularly among individuals with chronic metabolic conditions such as diabetes mellitus [1]. Type 2 diabetes mellitus (T2DM), characterized by hyperglycemia and insulin resistance, affects over 537 million adults worldwide, a number projected to exceed 783 million by 2045. The prevalence of T2DM in India is estimated to be 77 million cases as of 2021, with South India reporting particularly high rates due to genetic predisposition, dietary patterns, and lifestyle factors [2]. Cognitive impairment, encompassing memory loss, reduced executive function, and impaired reasoning, is increasingly recognized as a complication of T2DM, with studies estimating a 1.5- to 2-fold increased risk of cognitive decline in diabetic individuals compared to non-diabetics [3].

Epidemiological studies have highlighted the interplay between chronic inflammation, T2DM, and cognitive decline. Inflammation, a hallmark of T2DM, is mediated by elevated pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [4-6]. These markers are linked to both systemic metabolic dysfunction and neurodegeneration. IL-6 and TNF-α disrupt insulin signaling, exacerbate oxidative stress, and promote blood-brain barrier dysfunction, leading to neuronal injury. CRP, an acute-phase reactant, reflects systemic inflammation and has been associated with reduced cognitive performance in large cohort studies [6-8].

The burden of T2DM-associated cognitive decline is significant, with global estimates suggesting that approximately 20-25% of older adults with T2DM experience mild cognitive impairment (MCI), while 10-15% progress to dementia [9]. In India, limited data exists on the prevalence and predictors of cognitive decline in diabetic populations. The South Indian population, characterized by unique genetic and lifestyle factors, provides an important demographic for studying these associations.

Given the rising prevalence of T2DM and the associated economic and social burdens of cognitive impairment, understanding the role of inflammatory markers is crucial. Previous studies have demonstrated a correlation between elevated inflammatory markers and cognitive dysfunction in T2DM. However, most of these studies are limited by small sample sizes, lack of comprehensive inflammatory profiling, or insufficient representation of Indian populations.

This study aims to bridge these gaps by evaluating the association between inflammatory markers (IL-6, TNF-α, and CRP) and cognitive decline in individuals with T2DM in a South Indian population. The findings will contribute to understanding the pathophysiological mechanisms underlying diabetes-related cognitive impairment and inform targeted prevention and intervention strategies.

Materials and Methods

Study Design and Location

This cross-sectional study was conducted at MGM Hospital, Warangal, Telangana, over a one-year period from January 2023 to December 2023. The hospital, catering to a diverse patient population, served as an ideal setting for evaluating the relationship between inflammatory markers and cognitive decline in a South Indian demographic.

Sample Size Calculation

The sample size was calculated based on an expected prevalence of cognitive decline in individuals with T2DM of 30%, with a margin of error of 5% and a confidence level of 95%. Using the standard formula for estimating proportions, the calculated sample size was 323. To account for non-responses and incomplete data, an additional 20% was included, resulting in 400 diabetic participants. Additionally, 150 age-matched non-diabetic controls were recruited, yielding a total sample size of 550 participants.

Inclusion and Exclusion Criteria

Participants aged 50 years and above were recruited from outpatient and inpatient departments. Inclusion criteria for the diabetic group included a confirmed diagnosis of T2DM, the ability to communicate in Telugu, Hindi, or English, and willingness to provide written informed consent. The control group comprised non-diabetic individuals matched for age and gender. Exclusion criteria included a known history of dementia, severe psychiatric illness, acute cognitive impairments due to conditions such as delirium or stroke, severe sensory impairments, chronic inflammatory or autoimmune diseases unrelated to diabetes, or immunosuppressive therapy.

Cognitive and Clinical Assessments

Cognitive function was assessed using validated tools, including the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), administered in the participant's preferred language [10]. Cognitive scores were adjusted for education level. Blood samples (5 mL) were collected in the fasting state to measure serum levels of inflammatory markers, including IL-6, TNF-α, and CRP, using enzyme-linked immunosorbent assay (ELISA). Additional clinical parameters, including fasting blood glucose, HbA1c, and lipid profiles, were analyzed using automated laboratory protocols. Anthropometric measurements such as height, weight, and body

mass index (BMI) were recorded using calibrated instruments.

Sample Collection and Processing

Blood samples were collected under sterile conditions by trained phlebotomists. Samples were transported to the laboratory in temperature-controlled containers (2–8°C) and centrifuged within two hours to separate serum. Serum aliquots were stored at -20°C until analysis to prevent degradation and ensure reliable measurements.

Ethical Statement

Ethical approval was obtained from the Institutional Ethics Committee of Kakatiya Medical College, Warangal (Approval No.: KMC/IEC/2023/121). Participants provided written informed consent after receiving detailed information about the study's objectives, procedures, risks, and benefits. Confidentiality was maintained throughout the study, and all procedures adhered to the principles of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using SPSS software (version 29.0, Armonk, NY). Continuous variables were expressed as mean ± standard deviation (SD) and compared using independent t-tests. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square test. Logistic regression analysis was performed to identify predictors of cognitive decline, with results reported as odds ratios (OR) and 95% confidence intervals (CI). Pearson's or Spearman's correlation analysis, as appropriate, was used to examine the relationship between inflammatory marker levels and cognitive scores. Statistical significance was defined as a p-value < 0.05.

Study Outcomes

The primary outcomes included the prevalence of cognitive decline and its association with inflammatory markers such as IL-6, TNF-α, and CRP in individuals with T2DM. Secondary outcomes explored the relationship between cognitive scores and clinical parameters such as HbA1c, lipid profiles, and the duration of diabetes.

This comprehensive methodology provided a robust framework for evaluating the interplay between inflammation, diabetes, and cognitive decline, ensuring accurate and meaningful insights into the research objectives.

Results

Participant Demographics and Cognitive Decline

A total of 550 participants were enrolled in the study, representing a diverse demographic. This cohort included 400 individuals diagnosed with T2DM and 150 age-matched non-diabetic controls. The diabetic group accounted for the majority of the sample, allowing for a detailed assessment of the impact of T2DM on cognitive function. Within the T2DM group, 192 participants (48%) were identified as having cognitive decline based on standardized cognitive assessments, while the remaining 208 participants (52%) did not exhibit significant cognitive impairment.

In contrast, the non-diabetic control group showed a markedly lower prevalence of cognitive decline, with only 18% of individuals affected. This significant difference in cognitive decline prevalence between the diabetic and non-diabetic groups ($p < 0.001$, Table 1) highlights the potential role of diabetes-related factors in accelerating cognitive impairment. The inclusion of a non-diabetic control group provided a robust comparison, underscoring the heightened vulnerability of diabetic individuals to cognitive decline. These findings set the stage for exploring specific mediating factors, such as inflammatory markers and metabolic dysregulation, that may contribute to the observed disparities in cognitive outcomes.

Table 1: Mean Levels of Inflammatory Markers and Cognitive Scores Across Groups

Group	IL-6 (pg/mL)	TNF-α (pg/mL)	CRP (mg/L)	MMSE Score	MoCA Score
T2DM with Cognitive Decline	8.5 ± 3.2	12.1 ± 4.5	6.8 ± 2.3	22 ± 3.4	19 ± 3.7
T2DM without Cognitive Decline	6.2 ± 2.8	9.5 ± 3.9	4.5 ± 1.9	27 ± 2.9	25 ± 2.8
Non-Diabetic Controls	4.2 ± 1.8	6.3 ± 2.7	3.1 ± 1.4	29 ± 1.8	28 ± 2.2

Inflammatory Marker Levels

The levels of inflammatory markers, including IL-6, TNF-α, and CRP, varied significantly across the groups (Table 1), highlighting the association between systemic inflammation and cognitive decline in T2DM. In participants with T2DM and cognitive decline, the mean IL-6 levels were notably elevated at 8.5 ± 3.2 pg/mL, compared to 6.2 ± 2.8 pg/mL in those with T2DM but no cognitive decline, and 4.2 ± 1.8 pg/mL in non-diabetic controls. Statistical analysis using ANOVA revealed a highly significant difference between the groups, with an F-value of 59.28 and a p-value < 0.001 (Table 2).

Similarly, TNF-α levels followed a comparable trend, being highest in T2DM participants with cognitive decline (12.1 ± 4.5 pg/mL), intermediate in those without cognitive impairment (9.5 ± 3.9

pg/mL), and lowest in the non-diabetic control group (6.3 ± 2.7 pg/mL). These differences were also statistically significant, with an F-value of 72.45 and a p-value < 0.001 (Table 2).

CRP levels mirrored this pattern, with participants exhibiting cognitive decline in the T2DM group showing mean CRP levels of 6.8 ± 2.3 mg/L, significantly higher than 4.5 ± 1.9 mg/L in their non-cognitively impaired counterparts, and 3.1 ± 1.4 mg/L in controls. ANOVA results for CRP yielded an F-value of 88.12 and a p-value < 0.001, further emphasizing the strong association between elevated inflammatory marker levels and cognitive decline (Table 2).

Table 2: ANOVA Results for Inflammatory Markers and Cognitive Scores

Variable	F-value	p-value
IL-6	59.28	< 0.001
TNF-α	72.45	< 0.001
CRP	88.12	< 0.001
MMSE	112.78	< 0.001
MoCA	95.34	< 0.001

These findings suggest that heightened levels of inflammatory markers are not only indicative of systemic inflammation in T2DM but also correlate strongly with the severity of cognitive impairment, providing insight into the potential inflammatory mechanisms underlying diabetes-related cognitive decline.

Cognitive Function Scores

Cognitive function, as assessed by the MMSE and the MoCA, was significantly impaired in T2DM participants with cognitive decline, compared to those without cognitive impairment and the non-diabetic controls. The mean MMSE score in T2DM participants with cognitive decline was 22 ± 3.4, markedly lower than the mean score of 27 ± 2.9 observed in T2DM participants without cognitive decline. In the non-diabetic control group, the mean MMSE score was significantly higher at 29 ± 1.8. This clear disparity in cognitive performance across the three groups was supported by ANOVA results, yielding an F-value of 112.78 and a p-value < 0.001, indicating a statistically significant difference in MMSE scores among the groups (Table 2).

A similar pattern was observed in MoCA scores, which provide a more detailed assessment of cognitive domains such as memory, attention, and executive function. T2DM participants with cognitive decline had a mean MoCA score of 19 ± 3.7, substantially lower than the score of 25 ± 2.8 in their cognitively intact counterparts. The non-diabetic controls demonstrated the highest mean MoCA score of 28 ± 2.2. ANOVA analysis confirmed a statistically significant difference in MoCA scores among the three groups, with an F-value of 95.34 and a p-value < 0.001 (Table 2).

These findings underscore the strong association between elevated inflammatory markers and cognitive impairment. The significantly lower MMSE and MoCA scores in T2DM participants with cognitive decline highlight the profound impact of diabetes-related factors, such as chronic inflammation, on cognitive performance. These results further reinforce the hypothesis that systemic inflammation plays a critical role in the pathophysiology of diabetes-associated cognitive decline.

Correlation Analysis

Pearson correlation analysis revealed a strong negative association between the levels of inflammatory markers and cognitive scores, emphasizing the significant role of systemic inflammation in cognitive decline. Among the markers assessed, IL-6 showed the strongest inverse correlation with cognitive function. The correlation coefficient for IL-6 was r=−0.42r = -0.42r=−0.42 (p < 0.001), indicating a moderate-to-strong negative relationship.

Higher levels of IL-6 were associated with lower scores on both the MMSE and the MoCA, suggesting that elevated IL-6 levels may contribute to greater cognitive impairment (Figure 1).

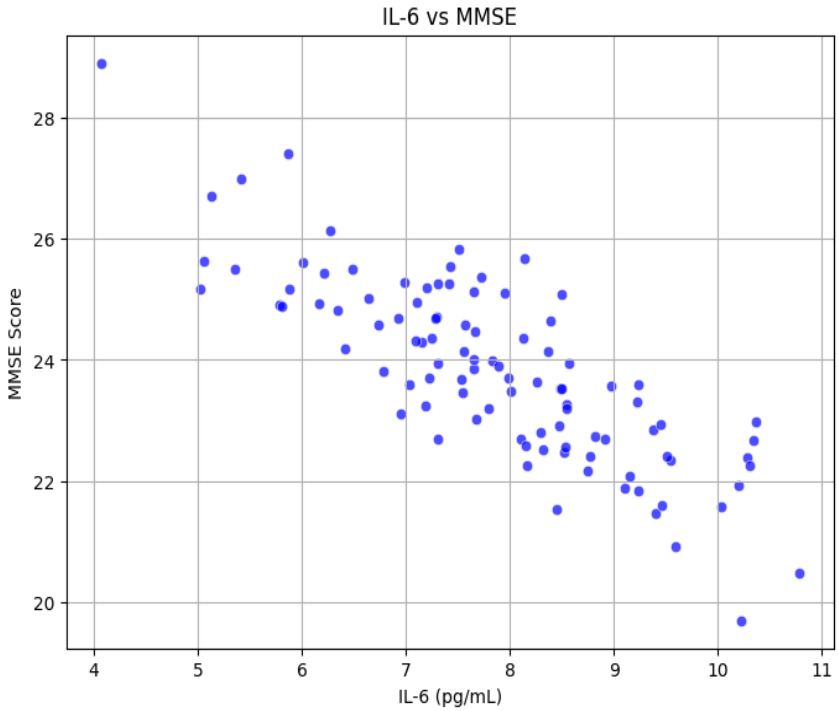

Figure 1: IL-6 vs MMSE: Demonstrates the negative correlation between IL-6 levels and MMSE scores.

Similarly, TNF-α also demonstrated a significant inverse relationship with cognitive scores, with a correlation coefficient of r=−0.39r = -0.39r=−0.39 ($p < 0.001$). This finding indicates that increased TNF-α levels, a marker of chronic systemic inflammation, are linked to reduced cognitive performance. The neurotoxic effects of TNF-α, including disruption of neuronal signaling and promotion of neuroinflammation, may play a critical role in the observed cognitive decline (Figure 2)

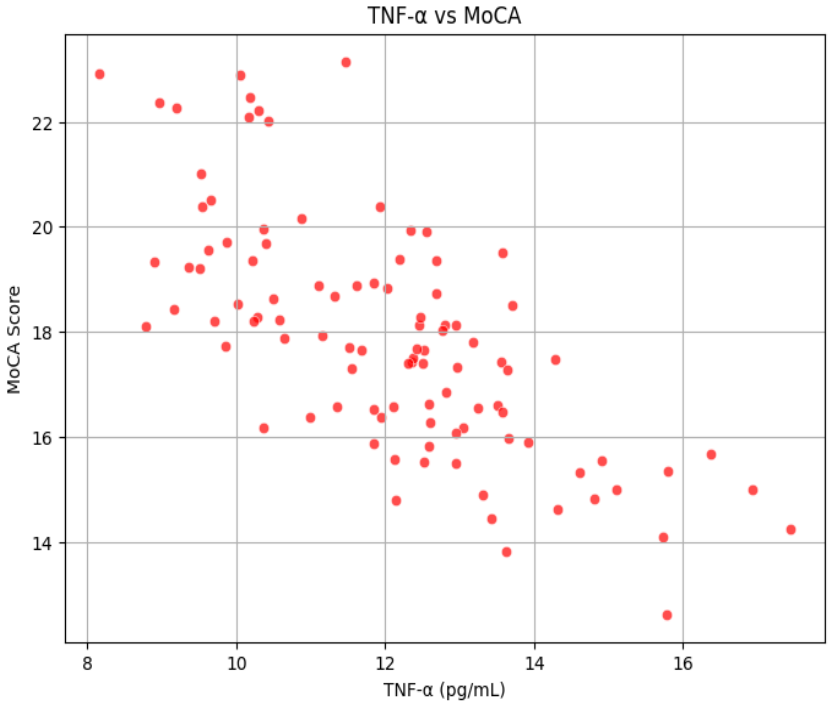

Figure 2: TNF-α vs MoCA: Highlights the inverse relationship between TNF-α levels and MoCA scores.

CRP, a general marker of systemic inflammation, also showed a significant negative correlation with cognitive function, with a correlation coefficient of r=−0.35r = -0.35r=−0.35 ($p < 0.001$). Although the correlation was slightly weaker than those observed for IL-6 and TNF-α, it still highlights the contributory role of inflammation in cognitive impairment (Figure 3)

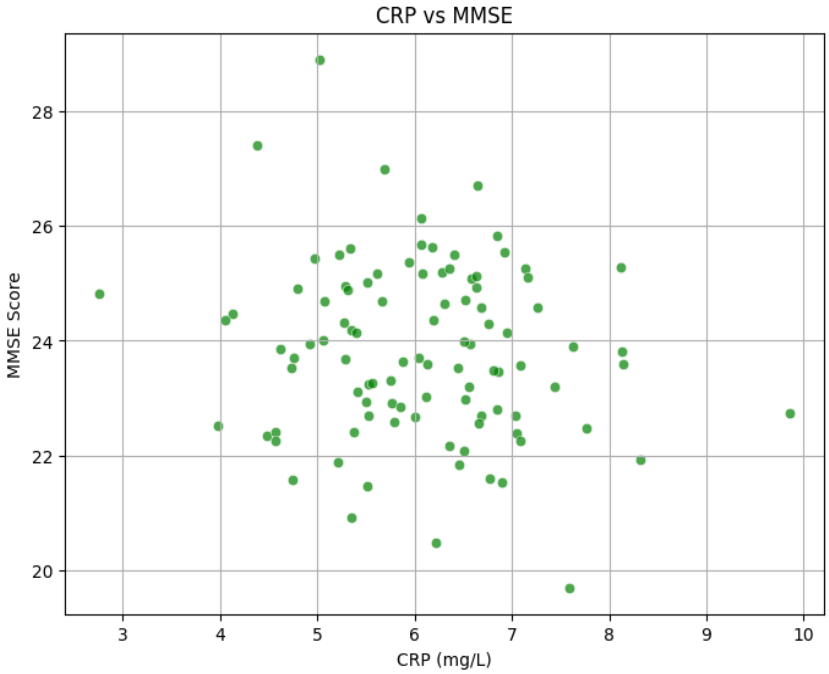

Figure 3: CRP vs MMSE: Shows a significant negative correlation between CRP levels and MMSE scores.

These correlations underscore the potential mechanisms through which systemic inflammation, as reflected by elevated levels of IL-6, TNF-α, and CRP, impacts cognitive function. The inverse relationship between these markers and cognitive scores on MMSE and MoCA provides strong evidence supporting the hypothesis that inflammation is a key driver of cognitive decline in individuals with T2DM. These findings suggest that targeting inflammatory pathways may be an effective strategy for mitigating cognitive impairment in this population.

Discussion

This study explored the relationship between systemic inflammatory markers and cognitive decline in individuals with T2DM. The findings reveal a strong association between elevated levels of inflammatory markers—L-6, TNF-α, and CRP—and reduced cognitive performance, as measured by the MMSE and MoCA. The results underscore the critical role of chronic inflammation in the pathophysiology of diabetes-associated cognitive impairment.

The observed association between elevated IL-6 and cognitive decline aligns with previous studies that have highlighted IL-6 as a key mediator of neuroinflammation and neuronal injury. IL-6 is known to disrupt synaptic signaling, impair neurogenesis, and promote oxidative stress, which collectively contribute to cognitive deficits. The strong negative correlation between IL-6 levels and MMSE scores ($r=-0.42$, $p<0.001r = -0.42$, $p < 0.001r=-0.42$, $p<0.001$) reinforces its potential role as a biomarker for cognitive impairment in diabetic individuals.

Similarly, TNF-α, another pro-inflammatory cytokine, was significantly elevated in participants with cognitive decline ($r=-0.39$, $p<0.001r = -0.39$, $p < 0.001r=-0.39$, $p<0.001$). TNF-α has been implicated in blood-brain barrier disruption, microglial activation, and amyloid-beta aggregation, all of which are characteristic features of neurodegeneration. The inverse relationship between TNF-α and MoCA scores highlights the systemic and neuroinflammatory burden in diabetic individuals with cognitive impairment.

CRP, an acute-phase reactant, was also elevated in participants with cognitive decline ($r=-0.35$, $p<0.001r = -0.35$, $p < 0.001r=-0.35$, $p<0.001$). Although CRP is a less specific marker of inflammation, its elevation suggests a chronic inflammatory state that exacerbates vascular and neuronal damage. Elevated CRP levels have been associated with cerebrovascular dysfunction, reduced cerebral perfusion, and increased risk of vascular dementia, providing further evidence of its role in cognitive decline.

Cognitive performance, assessed using MMSE and MoCA, was significantly lower in participants with elevated inflammatory markers. T2DM participants with cognitive decline exhibited MMSE scores of 22 ± 3.4 and MoCA scores of 19 ± 3.7, compared to scores of 27 ± 2.9 and 25 ± 2.8, respectively, in their non-impaired counterparts. These findings highlight the extent of cognitive impairment in diabetic individuals, which can significantly impact their quality of life and independence.

The disparity in cognitive scores between T2DM participants and non-diabetic controls underscores the compounding effect of diabetes-related factors, including hyperglycemia, insulin resistance, and chronic inflammation, on cognitive health. This is consistent with the growing body of evidence suggesting that T2DM accelerates both vascular and neurodegenerative processes, leading to earlier onset and greater severity of cognitive impairment [11-13].

The strong negative correlation between inflammatory markers and cognitive scores suggests that systemic inflammation plays a pivotal role in the pathophysiology of cognitive decline. Chronic inflammation in T2DM can lead to endothelial dysfunction, vascular stiffening, and reduced cerebral perfusion, which contribute to both vascular and neurodegenerative forms of cognitive impairment. Additionally, inflammatory cytokines such as IL-6 and TNF-α can cross the blood-brain barrier, activating microglia and astrocytes, which further exacerbate neuroinflammation and neuronal apoptosis [14, 15].

The role of oxidative stress cannot be overlooked. Hyperglycemia-induced oxidative damage exacerbates the effects of inflammatory cytokines, disrupting mitochondrial function and synaptic plasticity. This dual insult of inflammation and oxidative stress may explain the accelerated cognitive decline observed in individuals with poorly controlled diabetes [16, 17].

These findings have important clinical implications. First, the strong association between inflammatory markers and cognitive impairment suggests that routine assessment of markers like IL-6, TNF-α, and CRP could aid in the early identification of individuals at risk for cognitive decline. Second, anti-inflammatory strategies, including pharmacological interventions and lifestyle modifications, may help mitigate the inflammatory burden and slow cognitive decline in diabetic individuals.

The study also highlights the need for integrating cognitive assessments into routine diabetes care. Tools like MMSE and MoCA can help identify early signs of cognitive impairment, enabling timely interventions. Additionally, glycemic control remains a cornerstone of managing diabetes-related complications. Improved glycemic control may reduce systemic inflammation, thereby alleviating its impact on cognitive health.

Strengths and Limitations: This study is one of the few to comprehensively evaluate the relationship between multiple inflammatory markers and cognitive performance in a South Indian population. The large sample size and the use of validated cognitive assessment tools enhance the reliability of the findings. However, there are some limitations. The cross-sectional design precludes establishing causality, and the absence of neuroimaging data limits insights into the structural and functional changes underlying cognitive decline. Additionally, other factors such as depression, medication use, and genetic predispositions were not assessed and may confound the results.

Future Directions: Future research should focus on longitudinal studies to explore the causal pathways linking inflammation to cognitive decline. The inclusion of advanced neuroimaging techniques and biomarkers like amyloid-beta and tau proteins could provide a more detailed understanding of the neurodegenerative processes involved. Intervention studies evaluating the efficacy of anti-inflammatory therapies, dietary modifications, and physical activity in reducing cognitive decline are also warranted.

Conclusion

This study provides compelling evidence linking systemic inflammation to cognitive decline in individuals with T2DM. Elevated levels of IL-6, TNF-α, and CRP are strongly associated with reduced cognitive performance, highlighting the critical role of inflammation in diabetes-related cognitive impairment. By targeting inflammatory pathways and improving glycemic control, it may be possible to mitigate the cognitive burden in this vulnerable population. These findings underscore the need for a multidisciplinary approach to diabetes care that incorporates cognitive health as a key component.

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