SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pharmacy Practice

Evaluation of Neurodegenerative Burden in Patients with Type-2-Diabetes Mellitus in a Tertiary Care Centre

Sudipta Paul[1*], Jervin Arokiaraj I[1], Sundar A[1], Saurav Kumar[1], Dr. Geetha Jayaprakash[2], Dr. Deepika G[3]

[1]PharmD Intern, Acharya & BM Reddy College of Pharmacy, Bengaluru, Karnataka
[2]Associate Professor, Department of Pharmacy Practice, Acharya & BM Reddy College of Pharmacy, Bengaluru, Karnataka
[3]Assistant Professor, Department of Pharmacology, ESIC MC-PGIMSR & Model Hospital, Bengaluru, Karnataka

DOI: https://doi.org/10.36347/sasjm.2025.v11i11.005 | **Received:** 15.09.2025 | **Accepted:** 04.11.2025 | **Published:** 14.11.2025

***Corresponding author:** Sudipta Paul
PharmD Intern, Acharya & BM Reddy College of Pharmacy, Bengaluru, Karnataka

Abstract **Original Research Article**

Chronic hyperglycemia, arising from deficient insulin secretion, impaired insulin action, or both, induces profound metabolic dysregulation across carbohydrate, lipid, and protein pathways. Mounting clinical and experimental evidence underscores a compelling association between diabetes mellitus (DM), particularly type 2 diabetes, and neurodegenerative disorders such as dementia and Alzheimer's disease. The pathophysiological nexus involves chronic oxidative stress, low-grade inflammation, and insulin resistance, which collectively precipitate neuronal injury and cognitive deterioration. The present observational study sought to evaluate the prevalence of neurodegenerative burden among individuals with diabetes of more than six years' duration. Conducted in the inpatient department of General Medicine at ESI MC & PGIMSR, Rajajinagar, Bengaluru, the study encompassed 100 participants who met defined inclusion and exclusion criteria. Demographic characteristics, medical history, and biochemical parameters were documented using a structured questionnaire, while cognitive performance was assessed via the Mini-Mental State Examination (MMSE). Statistical analyses, encompassing descriptive and inferential methods, were performed using Microsoft Excel. Among the cohort, 52% were males and 48% females, predominantly within the 68–75-year age range. Approximately 30% had diabetes for 6–8 years, 33% exhibited normal fasting blood glucose, and 57% showed elevated random blood glucose levels. Hypertension emerged as the most prevalent comorbidity (47%). Cognitive assessment revealed that 52% had no impairment, 27% exhibited mild impairment, and 21% demonstrated severe cognitive decline. Statistically significant associations were observed between MMSE scores and both HbA1c ($H = 8.200$, $p = 0.017$) and triglyceride levels ($H = 6.641$, $p = 0.036$). These findings underscore that sustained hyperglycemia and dyslipidemia are pivotal contributors to neurocognitive impairment in chronic diabetics. Consequently, integrating routine cognitive screening with stringent glycemic and lipid control is imperative to attenuate neurodegenerative progression and improve long-term neurological and functional outcomes in diabetic populations.

Keywords: MMSE, Cognitive Assesment, Hyperglycemia, Dementia.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to defective insulin secretion, impaired insulin sensitivity, or both [1,2] Insulin, produced by pancreatic β-cells, is vital for glucose uptake and metabolic regulation. Its deficiency or resistance disrupts glucose homeostasis, leading to multi-organ damage involving the cardiovascular, renal, neural, and ocular systems [3]. The long-term metabolic imbalance contributes to significant morbidity and mortality, making diabetes one of the most prevalent and costly global health challenges [4,5].

According to the World Health Organization, diabetes affects hundreds of millions worldwide, with type 2 diabetes mellitus (T2DM) accounting for nearly 90% of cases [2]. The escalating prevalence is attributed to sedentary lifestyles, obesity, and poor dietary habits. Type 1 diabetes mellitus (T1DM), though less common, arises from autoimmune destruction of pancreatic β-cells, resulting in absolute insulin deficiency [1]. Despite differing etiologies, all forms of diabetes share the hallmark feature of chronic hyperglycemia, which triggers biochemical cascades leading to oxidative stress, inflammation, and vascular dysfunction [6,7].

Emerging evidence reveals a strong association between diabetes and neurodegenerative disorders (NDs), particularly Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia [3,8,9]. Prolonged hyperglycemia and insulin resistance induce oxidative stress, mitochondrial dysfunction, and advanced glycation end-product (AGE) accumulation, which impair neuronal metabolism and accelerate neurodegeneration [10,11]. Epidemiological studies indicate that individuals with T2DM have nearly twice the risk of developing Alzheimer's disease compared to non-diabetic counterparts [12,13], suggesting that metabolic dysregulation plays a crucial role in neuronal decline.

The brain, though representing only 2% of body mass, consumes about 20% of total glucose-derived energy. Thus, impaired glucose utilization has profound neurological consequences [6]. Neurons depend on a continuous energy supply for synaptic transmission, plasticity, and repair. Insulin receptors are abundantly expressed in the hippocampus and cerebral cortex—regions critical for learning and memory. Insulin resistance in these areas leads to reduced neuronal survival, altered neurotransmission, and increased amyloid-β deposition, linking diabetes mechanistically to Alzheimer's pathology [6,10,11].

Oxidative stress is a key mediator of diabetic neurodegeneration [7,9]. Hyperglycemia enhances the production of reactive oxygen species (ROS), overwhelming endogenous antioxidant defenses. The brain's high oxygen demand and lipid content render it particularly susceptible to oxidative injury. ROS-induced damage to lipids, proteins, and nucleic acids compromises neuronal integrity and triggers apoptosis. Mitochondrial dysfunction further amplifies this cycle, impairing ATP production and escalating neuronal death [14].

In parallel, chronic low-grade inflammation contributes to the neuropathology of diabetes [12,15]. Elevated pro-inflammatory cytokines—such as TNF-α and IL-6—disrupt the blood-brain barrier, activate microglia, and potentiate neuroinflammation [12]. Additionally, AGEs formed during hyperglycemia interact with their receptors (RAGE), promoting oxidative and inflammatory signaling that accelerates neuronal injury [16,17]. Vascular dysfunction further compounds these effects by reducing cerebral perfusion and inducing ischemic damage, thereby aggravating cognitive decline [22,23].

Metformin, a cornerstone therapy for T2DM, has attracted attention for its paradoxical neuroprotective and neurotoxic properties [36,38]. Through activation of AMP-activated protein kinase (AMPK), it improves metabolic balance and mitigates oxidative stress [21]. However, long-term therapy can induce vitamin B12 deficiency, associated with neuropathy and cognitive impairment [18,20]. These dual effects underscore the need for careful therapeutic evaluation in diabetic individuals at risk of neurodegeneration.

Lifestyle factors, dyslipidemia, and hyperuricemia further modulate the link between diabetes and brain health [40]. Elevated uric acid and reduced antioxidant enzyme activity exacerbate oxidative injury, while hypertension and endothelial dysfunction compromise cerebral circulation [22,23]. Consequently, comprehensive management must encompass not only glycemic control but also lipid, pressure, and oxidative balance [34].

Early detection of cognitive decline is vital in diabetic care. Screening tools such as the Mini-Mental State Examination (MMSE) and Verbal Fluency Test (VFT) are effective for assessing cognitive performance and detecting mild impairment [24,27,23]. Diminished scores in diabetic patients may signal early neurodegenerative changes, warranting timely intervention [43].

Ultimately, diabetes mellitus extends beyond metabolic dysregulation to encompass significant neurological consequences. The interplay between hyperglycemia, oxidative stress, inflammation, and vascular dysfunction establishes a pathological nexus leading to cognitive deterioration [3,5,9,13]. Effective prevention requires integrated metabolic and neurological management, combining optimal glycemic control, antioxidant support, and cognitive monitoring [39]. As research continues to unravel the molecular pathways connecting diabetes to neurodegeneration, it offers promising opportunities for early intervention and improved patient outcomes [43].

MATERIAL & METHODOLOGY

The study was carried out at the Inpatient Department of General Medicine, ESI MC & PGIMSR, Rajaji Nagar, Bengaluru. This was an observational cross-sectional study conducted over 6 months.

SAMPLE SIZE: A total of 100 subjects from the inpatient department of General Medicine were included in the study based on inclusion and exclusion criteria.

The sample size was determined using the formulae-
$N = Z^2 * P * (1-P) / m^2$

where, Z = Z value=1.96; P = prevalence; M = margin of error=5% (0.05); confidence interval =95%

Therefore, the Sample size (N) was found to be 100.

Inclusion Criteria:

a) Subjects with history of Diabetes Mellitus for more than 6 years with neurodegenerative complication.
b) Any gender

Exclusion Criteria:

a) Patient age group younger than 18 years of age
b) Individuals not willing to participate in the study

Source of Data:

The different sources of data were:

a) Patient's case profile form
b) One-to-one interview with the study subject
c) Validated questionnaire

Study Tools:

1. Self-designed patient's case profile form- A data collection form was designed to collect all the details which included the patient's demographic details, disease and other relevant information and the patient medication chart was reviewed on the basis of diabetes mellitus.
2. Mini Mental State Examination: SV (to identify cognitive impairment)
3. Verbal fluency test

Study Procedure:

- The subjects meeting inclusion and exclusion criteria were identified by the investigator.
- Patient's demographic details, social history, medical and medication history was collected by using the self-designed patient's case profile form
- MMSE-2: SV [Questioner] and Verbal fluency test were used in assessing the patient cognitive impairment
- The data so obtained was entered into a Microsoft excel sheet and statistical analysis was performed

ANALYSIS

All recorded data were entered using MS Excel software and analyzed. The statistical study included Kruskal- Walli's test, Anova test and chi-square test for determining the result.

RESULTS

This study included a total of 100 patients drawn from inpatient Department of General Medicine in ESIC MC & PGIMSR, Rajajinagar, Bengaluru who fulfilled the inclusion criteria and had provided informed consent to participate in the study during the study period of 3 months.

DISTRIBUTION OF PATIENTS BASED ON AGE GROUPS- Out of 100 patients, 26 patients (26%) belonged to age group of 68–75 years, 22 patients (22%) belonged to age group 60-67, 22 patients (22%) belonged to age group 52-59, 18 patients (18%) belonged to age group 44-51and 6 patients (6%) in two age groups 36-43 and 76-83.

Table 1: Distribution of patients based on age groups

Age groups (years)	Number of Patients (n)	Percentage (%)
36-43	6	6
44-51	18	18
52-59	22	22
60-67	22	22
68-75	26	26
76-83	6	6

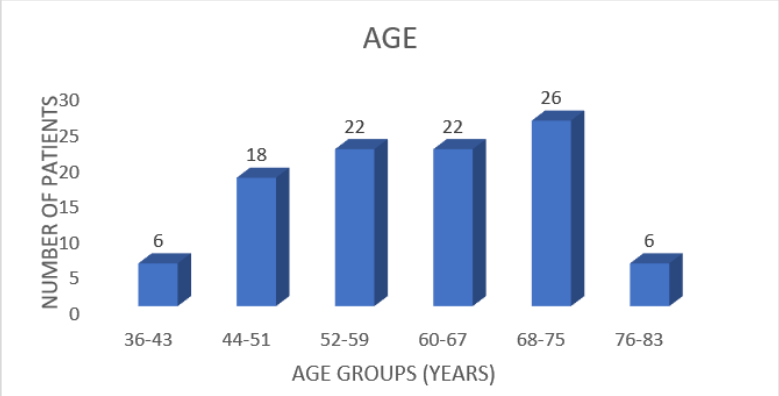

Figure 1: Distribution of Age

Distribution of Patient Based on Duration of Diabetes:

Out of 100 patients, majority of the patiens had diabetes for 6-8years and 27 patients had diabetes from 9-11 years, 14 patients had diabetes from 12-14 years, 11 patients had diabetes from 15-17 years and 12 patients had diabetes from 18-20 years.

Duration of Diabetes (in years)	Number of Patients
9-11	27
12-14	14
15-17	11
18-20	12
21-23	2
24-26	0
27-29	2
30-32	2

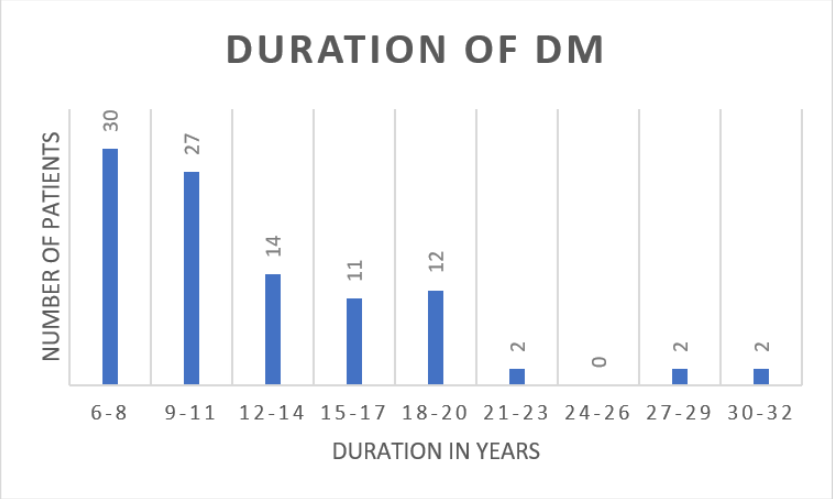

Figure 2: Distribution of patients based on duration of diabetes

Distribution of Patients by Gender:

Table 2: Distribution of patients by gender		
Gender	**Number of Patients (n)**	**Percentage (%)**
Male	52	52
Female	48	48
Total	**100**	**100**

Patients were distributed based on gender as shown in figure 2. Out of 100 patients included in the study,52 patients (52%) were males while 48 females (48%) contributed to the total number of patients enrolled in the study.

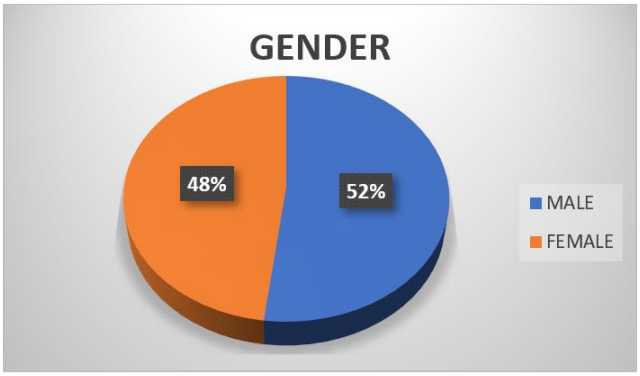

Figure 3: Distribution of Gender

Distribution of Patients Based on Social Habits

Out of 100 patients, 22 patients i.e. 22% had the habit of consuming alcohol while 16 patients i.e. 16% were smokers.

Social Habit	Yes	Percentage	No	Percentage

ALCOHOL	22	22	78	78
SMOKING	16	16	84	84

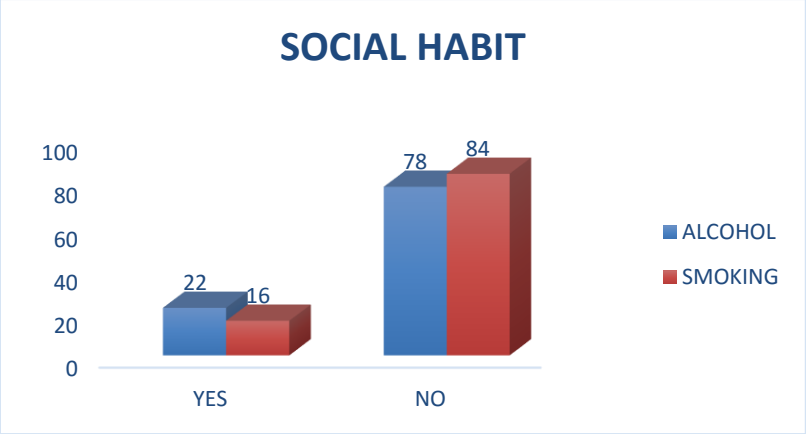

Figure 4: Distribution of patients based on social habits

Distribution of Patient Based on Fasting Blood Sugar:

Out of 100 patients, 33 patients had normal FBS levels and 23 patients had the FBS level above the normal level whereas 4 patients were prediabetic and for 40 patients the FBS level were not available.

Fasting Blood Sugar	Number of Patients
Normal	33
Pre diabetes	4
diabetes	23
Not Available	40

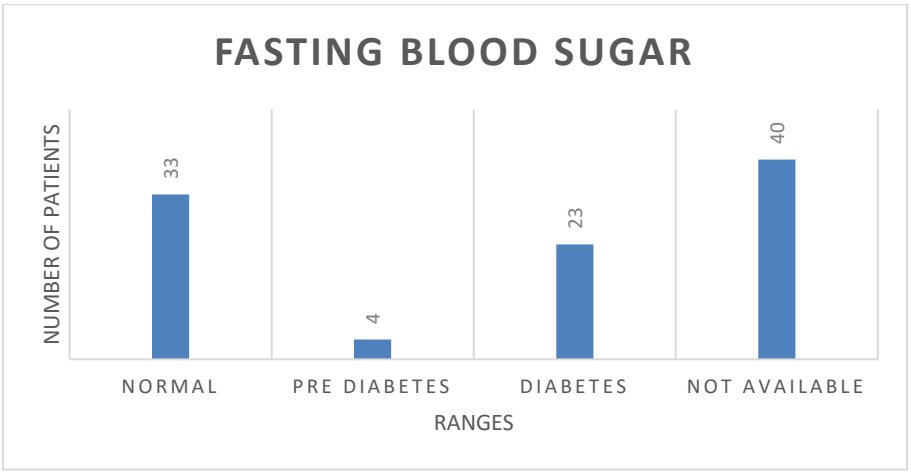

Figure 5: Distribution of patients based on Fating Blood Sugar

Distribution of Patient Based on Random Blood Sugar

Among 100 patients, 9 patients had normal RBS level and 57 patients had RBS above normal level and for 30 patients the RBS value was not available.

Random Blood Sugar	No of Patients
Normal	9
Pre-diabetes	2
Diabetes	57
Not Available	32

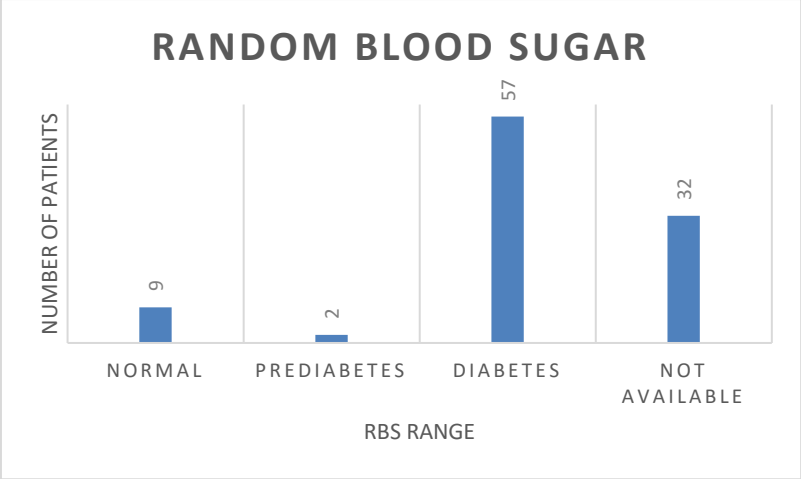

Figure 6: Distribution of patients based on Random Blood Sugar

Distribution of Patient Based on Triglycerides:

Out of 100 patients, 34 patients had normal triglycerides and 19 patients had higher triglycerides level and 2 patients had very high levels of triglycerides whereas 39 patients did not have their triglycerides value.

Triglycerides	No of Participants
Normal	34
BODERLINE -High	6
HIGH	19
VERY HIGH	2
NOT AVAILABLE	39

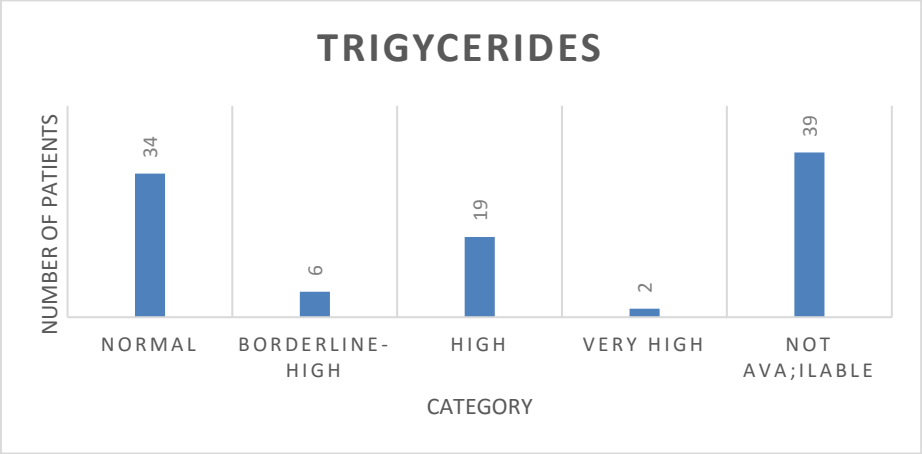

Figure 7: Distribution of patients based on triglycerides

Distribution of Patients Based on Hba1c

Out of 100 patients, 49 patients did not have normal HBA1C level whereas 2 patients had normal HBA1C level and for 46 patients the HBA1C level was not available.

HBA1C	No of Patients
NORMAL	2
PREDIABETES	3
DIABETES	49
NOT AVAILABLE	46

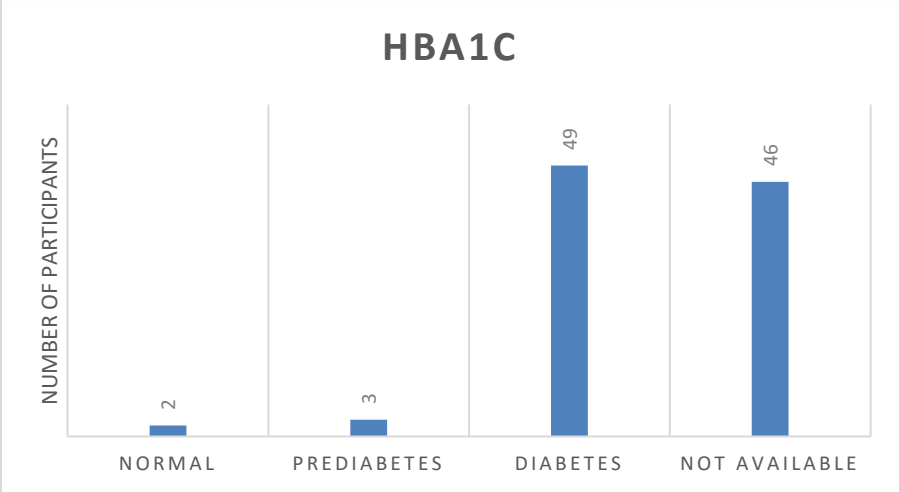

Figure 8: Distribution of population based on HBA1C

Distribution of Patients Based on Blood Pressure (Jnc-7 Classification):

Out of 100 patients, 37 patients were in pre-hypertension stage and 35 patients had normal range of BP, whereas 22 patients were in stage-1 hypertension stage and 6 patients belonged to stage-2 hypertension condition.

Category	No of Participants
Normal	35
PRE-HYPERTENSION	37
STAGE-1	22
STAGE-2	6

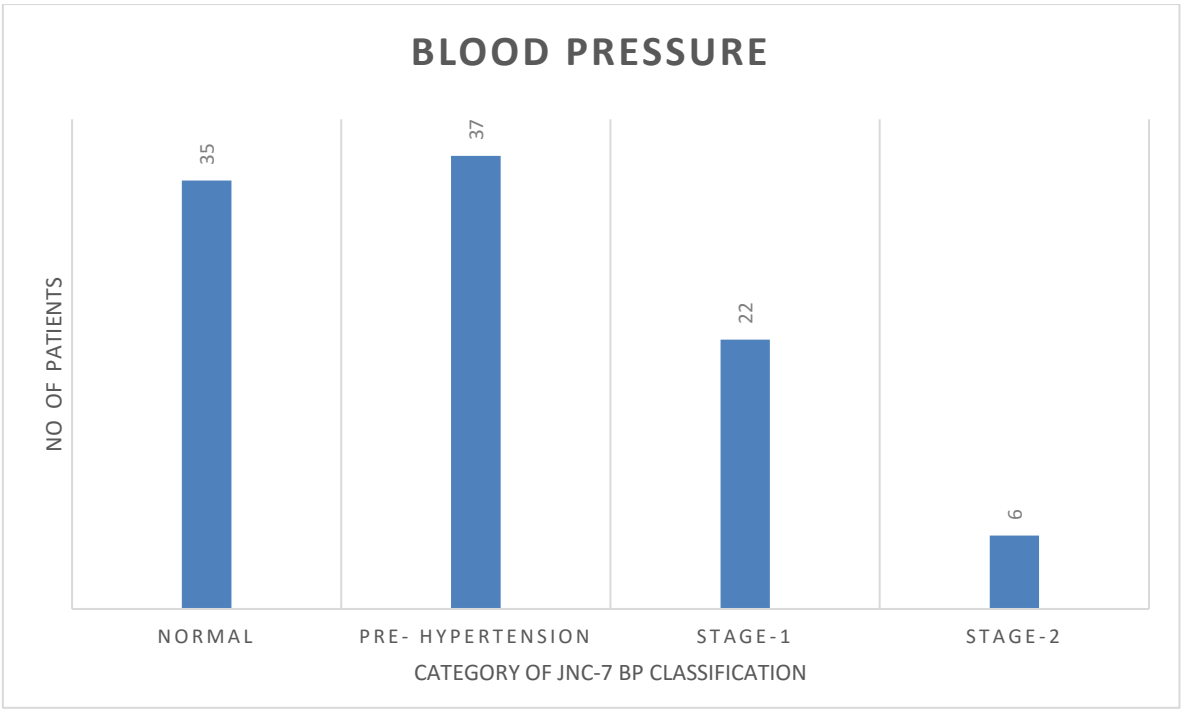

Figure 9: Distribution of patients based on blood pressure

Distribution of Patients Based on Comorbidity

The most commonly observed comorbidity in the study was hypertension. 47 patients i.e. 47% were experiencing hypertension. The least number of patients were 1 i.e.(1%) having Iron deficiency anemia, Tuberculosis, Psychosis, Parkinsonism (1.16%) as shown in Figure 5.

Table 5: Distribution of patients based on comorbidity

Types of complications	Number of patients(n)	Percentage (%)
Hypertension	47	47%
Chronic Kidney Disease	7	7%
IHD	8	8%
Thyroid	6	6%
IDA	1	1%
Tuberculosis	1	1%
Ischemic Heart Disease	8	8%
Dyslipidemia	2	2%
Psychosis	1	1%
Parkinsonism	1	1%
Asthma	2	2%
CLD	2	2%

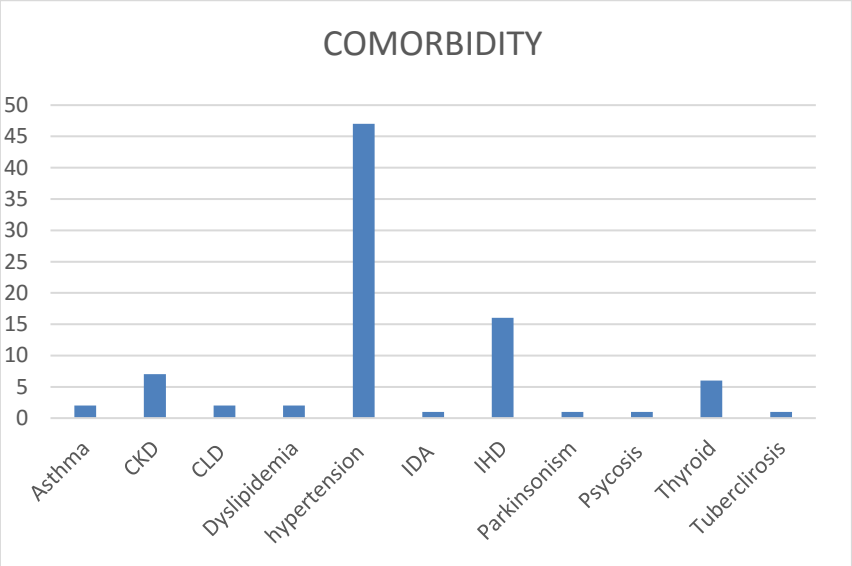

Figure 10: Distribution of patients based on comorbidity

Distribution of Patient S Based on Mmse

According to MMSE, out of 100 patients, 52 patients (52%) did not have cognitive impairment whereas 27 patients had mild cognitive impairment and 21 patients had severe cognitive impairment**.**

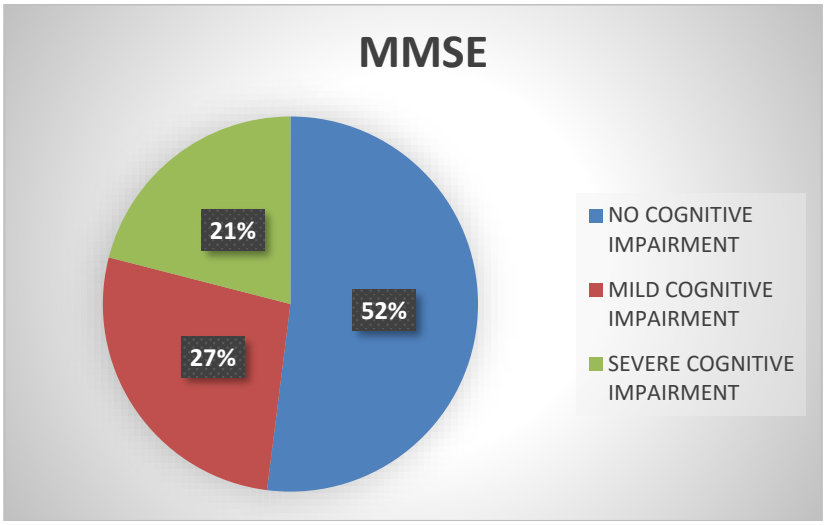

Figure 11: Distribution of patients based on MMSE score

Distribution of Patients Based on Verbal Fluency Test

According to verbal fluency test, 78 patients(78%) were normal and 22 patients (22%) have concerns of cognitive impairment.

Verbal Fluency Test	Normal	Concern
Percentage	78%	22%

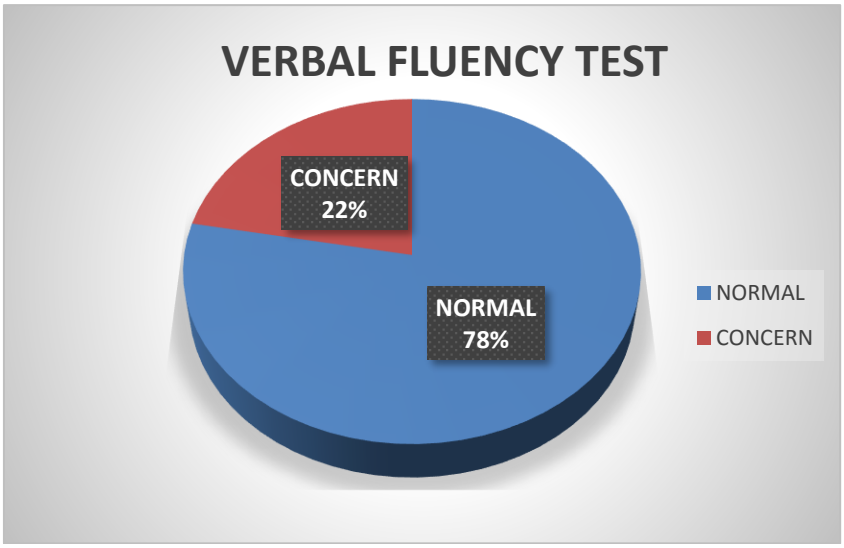

Figure 12: Distribution of patients based on verbal fluency test

Statistical Analysis

Association of Gender and Cognitive Impairment

The Pearson Chi-Square value is 0.618 with 2 degrees of freedom, and the asymptotic significance (p-value) is 0.734. This high p-value indicates that there is no statistically significant association between gender and cognitive impairment levels. The distribution of cognitive impairments (mild, no, and severe) does not significantly differ between males and females.

	COGNITIVE IMPAIRMENTS			TOTAL
Gender	**Mild Cognitive Impairments**	**Severe Cognitive Impairments**	**No Cognitive Impairments**	
FEMALE	14	11	23	48
MALE	13	10	29	52
TOTAL	27	21	52	100

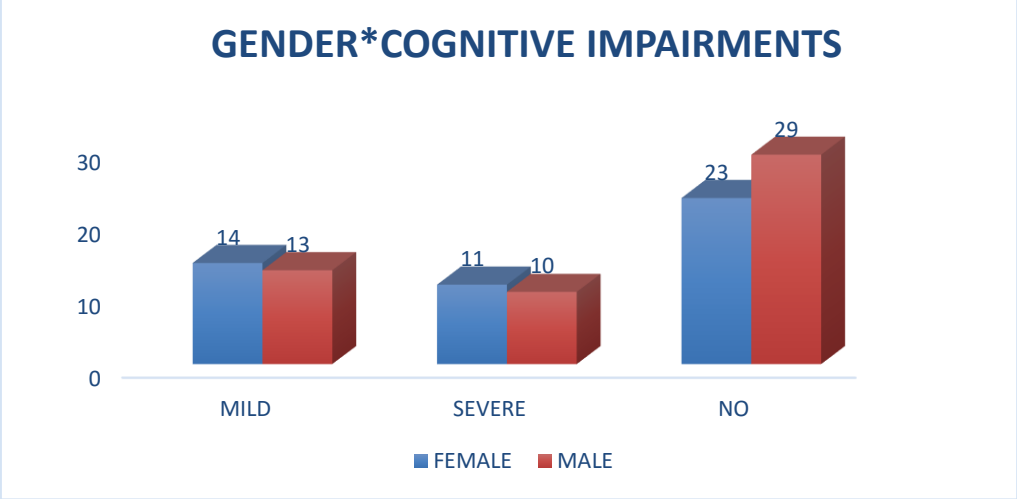

Figure 13: **Association of gender and cognitive impairment**

Association of Smoking and Cognitive Impairments

The Pearson Chi-Square value is 0.188 with 2 degrees of freedom, and the p-value is 0.910. The p-value

is much greater than 0.05, suggesting that there is no significant relationship between smoking status and cognitive impairment. The prevalence of cognitive impairments among smokers and non-smokers does not differ significantly.

Smoking		Cognitive Impairments			Total
		MILD	SEVERE	NO	
No	Count	22	18	44	84
	%Within Smoking	26.2%	21.4%	52.4%	100%
Yes	Count	5	3	8	16
	%Within Smoking	31.3%	18.8%	50%	100%
Total	Count	27	21	52	100
	%Within Smoking	27%	21%	52%	100%

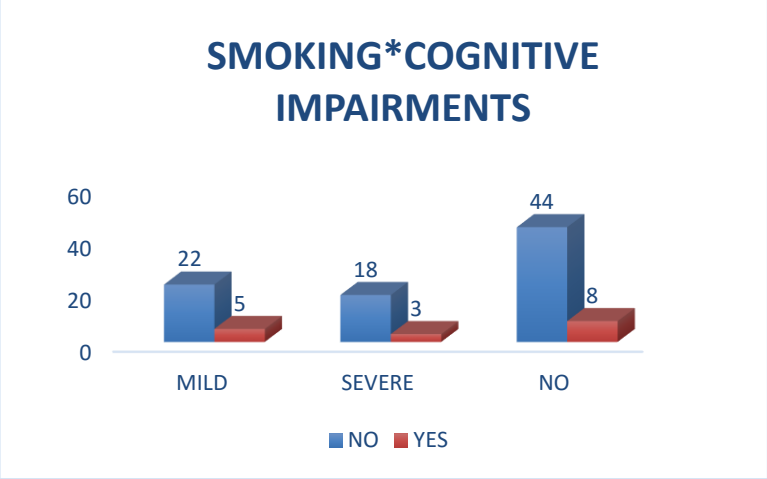

Figure 14: Association of smoking and cognitive impairments

Association of Alcohol and Cognitive Impairment

The Pearson Chi-Square value is 0.063 with 2 degrees of freedom, and the p-value is 0.969. This extremely high p-value indicates no significant association between alcohol consumption and cognitive impairments. The data does not support a significant difference in cognitive impairment levels between individuals who consume alcohol and those who do not.

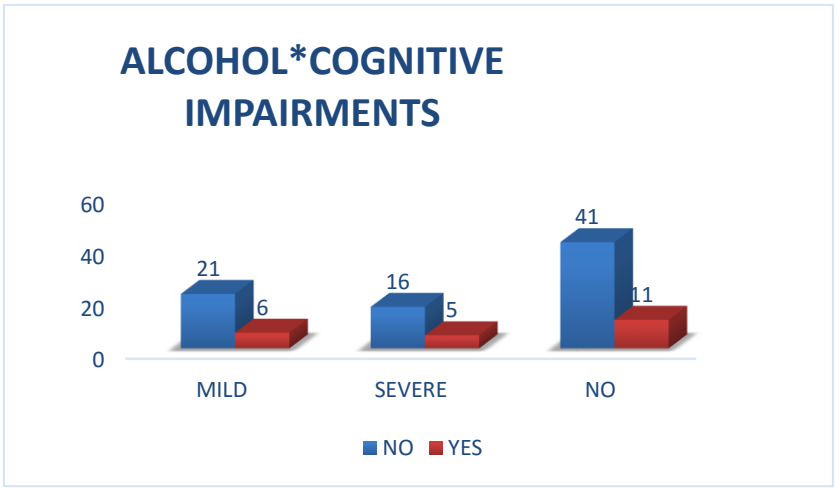

Figure 15: Association of alcohol and cognitive impairment

Association of Mmse Score and Cognitive Impairment

The Pearson Chi-Square value is 83.658 with 2 degrees of freedom, and the asymptotic significance (p-value) is less than 0.001. This p-value is significantly below the common threshold of 0.05, indicating a strong statistical association between the SCORE categories and cognitive impairment levels.

The Kruskal-Walli's test shows a highly significant difference in MMSE scores is observed among the cognitive impairment groups (H = 82.621, p

< 0.001), reflecting substantial variations in cognitive function across the groups.

Association of Rbs and Cognitive Impairment

The ANOVA for RBS shows no significant differences between the three cognitive impairment groups (Mild, No Cognitive Impairment, Severe) with an F-value of 0.489 and a p-value of 0.615. This indicates that the mean RBS levels are similar across all impairment levels.RBS levels does not significantly affect cognitive impairment.

Association of Fbs and Cognitive Impairment

The Kruskal-Wallis test shows no significant difference in FBS levels among the cognitive impairment groups (H = 1.182, p = 0.554), suggesting that FBS level does not significantly affect the level of cognitive impairment.

Association of Hba1c And Cognitive Impairment

The Kruskal-Walli's test shows significant differences in HBA1C level among the cognitive impairment groups (H = 8.200, p = 0.017), indicating that HBA1C levels have significant effect on the severity of cognitive impairment.

Association of Triglycerides and Cognitive Impairment

The Kruskal-Wallis test shows a significant difference in triglyceride levels among the cognitive impairment groups (H = 6.641, p = 0.036), indicating that triglyceride levels significantly affect the cognitive impairment levels.

Association of Duration of Dm with Cognitive Impairment

The Kruskal-Wallis test shows no significant difference between in the duration of diabetes and the cognitive impairment (H = 0.682, p = 0.711), indicating that the length of time with diabetes does not significantly affect cognitive impairment levels.

DISCUSSION

The results of this study provide valuable insights into the demographic and clinical characteristics of patients with diabetes, highlighting significant associations with cognitive impairment. This discussion contextualizes our findings with existing literature, underscoring key observations while addressing the implications for clinical practice.The age distribution in this cohort reflects a higher prevalence of diabetes among older adults, particularly those aged 68–75 years, which is consistent with other studies that have shown age as a significant risk factor for diabetes and its complications (Gonzalez et al., 2019).[30] The gender distribution, with a slight male predominance (52% male vs. 48% female), aligns with findings from the Diabetes Control and Complications Trial, which reported similar demographic patterns (DCCT Research Group, 1993).[29] Our study identified that 27% of participants experienced mild cognitive impairment and 21% had severe impairment. This prevalence is consistent with findings from the Chicago Health and Aging Project, which demonstrated that cognitive decline is prevalent in older adults with diabetes (Biessels & Reagan, 2015) [6] The association between cognitive impairment and diabetes duration was not significant in our analysis, corroborating studies that indicate cognitive decline may not always correlate directly with diabetes duration but rather with metabolic control (Luchsinger *et al.*, 2007).[31] The assessment of cognitive impairment using the Mini-Mental State Examination (MMSE) revealed that 52% of the 100 patients studied did not exhibit cognitive impairment, while 27% showed mild impairment and 21% demonstrated severe cognitive impairment. These findings highlight a significant prevalence of cognitive decline among patients, particularly in the context of diabetes, which is often linked to various neurological complications. The distribution of cognitive impairment observed in our study is consistent with findings from another research. For instance, a study by Biessels and Reagan (2015) found that cognitive impairment is prevalent in individuals with diabetes, particularly in older adults. Their research indicated that cognitive deficits are frequently observed in approximately 30-50% of diabetic patients, similar to the 48% observed in our study experiencing some degree of cognitive impairment [6] Moreover, a systematic review by Luchsinger *et al.,* (2007) reported that the risk of cognitive impairment and dementia increases significantly in patients with diabetes, especially with poor glycemic control. This is supported by our finding that even among those with no cognitive impairment, monitoring is crucial, as cognitive decline may be more subtle and requires early detection for timely intervention. [31] Our results indicate a notable proportion of patients (21%) with severe cognitive impairment, which aligns with research conducted by Whitmer et al. (2005), who reported that diabetes increases the risk of both mild and severe cognitive decline. Their study suggested that vascular factors associated with diabetes, such as hypertension and dyslipidemia, contribute significantly to cognitive deterioration. [34] In contrast, a study by Roriz-Filho *et al.,* (2009) found a lower prevalence of severe cognitive impairment among diabetic patients, suggesting that regional differences and variations in sample characteristics can lead to differing prevalence rates. The discrepancies highlight the importance of considering local demographics and healthcare contexts when interpreting cognitive impairment rates in diabetes patients. [36] The significant number of patients exhibiting cognitive impairment in our study underscores the need for regular cognitive assessments as part of diabetes management. Clinicians should be aware of the potential for cognitive decline in their patients and incorporate cognitive screenings into routine evaluations. Early identification of cognitive impairment can lead to interventions that may mitigate further decline and improve overall quality of life. The significant

association found between HbA1c levels and cognitive impairment (H = 8.200, p = 0.017) is particularly noteworthy. Several studies have demonstrated that poor glycemic control is linked to an increased risk of cognitive decline, potentially through mechanisms such as vascular damage and neurodegeneration (Whitmer *et al.*, 2005). However, our study did not find a significant association between fasting blood sugar (FBS) or random blood sugar (RBS) levels and cognitive impairment. This suggests that HbA1c, as a long-term marker of glycemic control, may be a better predictor of cognitive health than short-term measures. [34] The significant relationship between triglyceride levels and cognitive impairment (H = 6.641, p = 0.036) highlights the importance of lipid management in this population. High triglycerides are associated with an increased risk of cardiovascular disease, which in turn impacts brain health (Moran *et al.*, 2016). This finding suggests that addressing dyslipidemia could be critical in mitigating cognitive decline in patients with diabetes [32]. Our findings regarding smoking and alcohol consumption showed no significant association with cognitive impairment. This is in line with some studies suggesting that while these factors can impact cognitive function, their effects may be confounded by other health conditions or lifestyle factors (Takahashi *et al.*, 2020). Continued investigation into the multifactorial nature of cognitive decline in diabetes is essential.[33] Hypertension emerged as a common comorbidity, present in 47% of our patients, which aligns with literature indicating a high prevalence of hypertension in individuals with diabetes (Zoungas *et al.*, 2014). The interplay between diabetes and hypertension emphasizes the need for integrated management strategies to address both conditions, potentially reducing the risk of cognitive impairment.[35]

CONCLUSION

In conclusion, our study highlights a significant prevalence of cognitive impairment among type-2 diabetic patients, particularly in the older demographic, with 27% experiencing mild impairment and 21% facing severe cognitive decline. These findings align with existing literature, reaffirming that cognitive deficits are a critical concern within this population. Notably, the relationship between HbA1c levels and cognitive health underscores the importance of long-term glycemic control as a key factor in mitigating cognitive decline. Additionally, the significant association between triglyceride levels and cognitive impairment points to the necessity of addressing dyslipidemia in diabetes management.The high prevalence of hypertension among our participants further emphasizes the need for integrated care approaches that address both diabetes and its common comorbidities. Regular cognitive assessments should be incorporated into routine diabetes care to facilitate early detection and intervention, potentially enhancing patient outcomes and quality of life. Overall, this study underscores the multifaceted nature of cognitive decline in type-2 diabetes, indicating that both metabolic control and vascular health are critical areas for intervention. Future research should continue to explore these associations, focusing on tailored strategies that can effectively manage both diabetes and cognitive health.

ACKNOWLEDGMENTS

We sincerely thank all those who contributed directly or indirectly to the success of this work. We are grateful to Almighty God for granting us strength, wisdom, and health to complete this study. We extend our gratitude to Principal, Management and staff of Acharya & BM Reddy College of Pharmacy, Bengaluru, for providing the infrastructure and support required for this work. co-guide Department of medical oncology ESIC MC & PGIMSR, for support, guidance, and encouragement.

REFERENCES

1. Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, et al. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother [Internet]. 2023;168(115734):115734. Available from: http://dx.doi.org/10.1016/j.biopha.2023.115734
2. Alam S, Hasan MK, Neaz S, Hussain N, Hossain MF, Rahman T. Diabetes mellitus: Insights from epidemiology, biochemistry, risk factors, diagnosis, complications and comprehensive management. Diabetology [Internet]. 2021;2(2):36–50. Available from: http://dx.doi.org/10.3390/diabetology2020004
3. Nasrolahi A, Mahmoudi J, Noori-Zadeh A, Haghani K, Bakhtiyari S, Darabi S. Shared pathological mechanisms between diabetes mellitus and neurodegenerative diseases. Curr Pharmacol Rep [Internet]. 2019;5(4):219–31. Available from: http://dx.doi.org/10.1007/s40495-019-00191-8
4. Luna R, Talanki Manjunatha R, Bollu B, Jhaveri S, Avanthika C, Reddy N, et al. A comprehensive review of neuronal changes in diabetics. Cureus [Internet]. 2021;13(10):e19142. Available from: http://dx.doi.org/10.7759/cureus.19142
5. Santiago JA, Karthikeyan M, Lackey M, Villavicencio D, Potashkin JA. Diabetes: a tipping point in neurodegenerative diseases. Trends Mol Med [Internet]. 2023;29(12):1029–44. Available from:https://linkinghub.elsevier.com/retrieve/pii/S1471491423002204
6. Biessels GJ, Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. Nat Rev Neurosci [Internet]. 2015 [cited 2024 Sep 28];16(11):660–71. Available from: https://www.nature.com/articles/nrn4019
7. Mule NK, Singh JN. Diabetes mellitus to neurodegenerative disorders: Is oxidative stress fueling the flame? CNS Neurol Disord Drug Targets [Internet]. 2018;17(9):644–53. Available from:

http://dx.doi.org/10.2174/1871527317666180809092359
8. Kowluru RA, Chan P-S. Oxidative stress and diabetic retinopathy. Exp Diabetes Res [Internet]. 2007;2007:43603. Available from: http://dx.doi.org/10.1155/2007/43603
9. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res [Internet]. 2010;107(9):1058–70. Available from: http://dx.doi.org/10.1161/CIRCRESAHA.110.223545
10. Talbot, K., Wang, H. Y., Kazi, H., et al. (2012). Demonstrating that Alzheimer pathology begins in the insulin-resistant brain. Journal of Clinical Investigation, 122(4), 1325-1336. [Link to Article](https://doi.org/10.1172/jci58603) [Internet]. Bing. [cited 2024 Sep 28].
11. De la Monte, S. M. (2012). Type 3 diabetes is sporadic Alzheimer's disease: mini-review. Frontiers in Aging Neuroscience, 4, 128. [Link to Article](https://doi.org/10.3389/fnagi.2012.00128 [Internet]. Bing. [cited 2024 Sep 28].Availablefrom:https://www.bing.com/search?pglt=41&q=11+de+la+Monte%2C+S.+M.+(2012).+Type+3+diabetes+is+sporadic+Alzheimer%E2%80%99s+disease%3A+minireview.+Frontiers+in+Aging+Neuroscience%2C+4%2C+128.+%5BLink+to+Article%5D(https%3A%2F%2Fdoi.org%2F10.3389%2Ffnagi.2012.00128&cvid=83b8c1b18e3242e6994b2c528297bf18&gs_lcrp=EgZjaHJvbWUyBggAEEUYOdIBCDE5NjZqMGoxqAIIsAIB&FORM=ANNTA1&PC=U531
12. Hotamisligil GS. Inflammation and metabolic disorders. Nature [Internet]. 2006;444(7121):860–7. Available from: http://dx.doi.org/10.1038/nature05485
13. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis [Internet]. 2016;1863(5):1037–45. Available from: http://dx.doi.org/10.1016/j.bbadis.2016.04.017
14. Andreux PA, Houtkooper RH, Auwerx J. Pharmacological approaches to restore mitochondrial function. Nat Rev Drug Discov [Internet]. 2013;12(6):465–83. Available from: http://dx.doi.org/10.1038/nrd4023
15. Diabetesjournals.org. [cited 2024 Sep 28]. Available from: https://diabetesjournals.org/diabetes/article/58/4/773/117/From-the-Triumvirate-to-the-Ominous-Octet-A-New
16. Ramasamy R, Vannucci SJ, Yan SSD, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology [Internet]. 2005;15(7):16R-28R. Available from: http://dx.doi.org/10.1093/glycob/cwi053
17. Li J, Liu D, Sun L, Lu Y, Zhang Z. Advanced glycation end products and neurodegenerative diseases: Mechanisms and perspective. J Neurol Sci [Internet]. 2012;317(1–2):1–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022510X12001013
18. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin
19. B12 deficiency: An association to bear in mind. World J Diabetes [Internet]. 2021;12(7):916–31. Available from: http://dx.doi.org/10.4239/wjd.v12.i7.916
20. Sciencedirect.com. [cited 2024 Sep 29]. Available from: https://www.sciencedirect.com/science/article/abs/pii
21. Tiwari A, Kumar Singh R, Satone PD, Meshram RJ. Metformin-induced vitamin B12 deficiency in patients with type-2 diabetes mellitus. Cureus [Internet]. 2023;15(10):e47771. Available from: http://dx.doi.org/10.7759/cureus.47771
22. Barinaga M. Metformin and neurodegenerative diseases: Current perspectives. Frontiers in Pharmacology [Internet]. 2021;12. Available from: http://dx.doi.org/10.3389/fphar.2021.564487
23. Haan MN. Hypertension and cognitive decline in older adults: a review of the literature. Journal of Hypertension [Internet]. 2008;26(9):1639–48. Available from: http://dx.doi.org/10.1097/HJH.0b013e3283077e57
24. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet [Internet]. 2005;365(9455):217 Available from: http://dx.doi.org/10.1016/S0140-6736(05)17741-1
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res [Internet]. 1975;12(3):189–98. Available from: http://dx.doi.org/10.1016/0022-3956(75)90026-6
26. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc [Internet]. 1992;40(9):922–35. Available from: http://dx.doi.org/10.1111/j.1532-5415.1992.tb01992.x
27. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res [Internet]. 2008;43(4):411–31. Available from: http://dx.doi.org/10.1016/j.jpsychires.2008.04.014
28. JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia [Internet]. 2004;42(9):1212–22. Available from: http://dx.doi.org/10.1016/j.neuropsychologia.2004.02.001
29. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front Psychol [Internet]. 2014;5:772. Available from:

https://psycnet.apa.org/fulltext/2014-44734-001.pdf
30. Ruff RM, Light RH, Parker SB, Levin HS. The psychological construct of word fluency. Brain Lang [Internet]. 197;57(3):394–405. Available from: https://linkinghub.elsevier.com/retrieve/pii/S00939 34X97917557
31. Diabetesjournals.org. [cited 2024 Sep 29]. Available from: https://diabetesjournals.org/care/article/37/1/9/3178 9/The-Diabetes-Control-and-Complications-Trial
32. Longo M, Bellastella G, Maiorino MI, Meier JJ, Esposito K, Giugliano D. Diabetes and aging: From treatment goals to pharmacologic therapy. Front Endocrinol (Lausanne) [Internet]. 2019;10:45. Available from: http://dx.doi.org/10.3389/fendo.2019.00045
33. Luchsinger JA. Type 2 diabetes, related conditions, in relation and dementia: an opportunity for prevention? J Alzheimers Dis [Internet]. 2010;20(3):723–36. Available from: http://dx.doi.org/10.3233/JAD-2010-091687
34. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ [Internet]. 2005;330(7504):1360. Available from: http://dx.doi.org/10.1136/bmj.38446.466238.E0
35. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med [Internet]. 2014;371(15):1392–406. Available from: http://dx.doi.org/10.1056/NEJMoa1407963
36. Madhusudhanan J, Suresh G, Devanathan V. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. Brain Behav [Internet]. 2020;10(5):e01577. Available from: http://dx.doi.org/10.1002/brb3.1577
37. Kuan Y-C, Huang K-W, Lin C-L, Hu C-J, Kao C-H. Effects of metformin exposure on neurodegenerative diseases in elderly patients with type 2 diabetes mellitus. Prog Neuropsychopharmacol Biol Psychiatry [Internet]. 2017;79(Pt B):77–83. Available from: http://dx.doi.org/10.1016/j.pnpbp.2017.06.002
38. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, Rábano A, Cafini F, Pallas-Bazarra N, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med [Internet]. 2019;25(4):554–60. Available from: http://dx.doi.org/10.1038/s41591-019-0375-9
39. Rotermund C, Machetanz G, Fitzgerald JC. The therapeutic potential of metformin in neurodegenerative diseases. Front Endocrinol (Lausanne) [Internet]. 2018;9:400. Available from: http://dx.doi.org/10.3389/fendo.2018.00400
40. Cholerton B, Baker LD, Montine TJ, Craft S. Type 2 diabetes, cognition, and dementia in older adults: Toward a precision health approach. Diabetes Spectr [Internet]. 2016;29(4):210–9. Available from: http://dx.doi.org/10.2337/ds16-0041
41. S Roriz-Filho J, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves MLF, et al. (Pre)diabetes, brain aging, and cognition. Biochim Biophys Acta [Internet]. 2008;1792(5):432–43. Available from: http://dx.doi.org/10.1016/j.bbadis.2008.12.003
42. Reinke C. The effect of diabetes in the multifaceted relationship between education and cognitive function. BMC Public Health [Internet]. 2024;24(1):2584. Available from: http://dx.doi.org/10.1186/s12889-024-20156-x
43. Trento M, Charrier L, Salassa M, Merlo S, Passera P, Cavallo F, et al. Depression, anxiety and cognitive function in patients with type 2 diabetes: an 8-year prospective observational study. Acta Diabetol [Internet]. 2015;52(6):1157–66. Available from: http://dx.doi.org/10.1007/s00592-015-0806-0
44. Dove A, Shang Y, Xu W, Grande G, Laukka EJ, Fratiglioni L, et al. The impact of diabetes on cognitive impairment and its progression to dementia. Alzheimers Dement [Internet]. 2021;17(11):1769–78. Available from: http://dx.doi.org/10.1002/alz.12482