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Association of Diabetes mellitus with cognitive impairment in neuropathy

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Abstract
This review paper explores the complex interplay between diabetes mellitus, neuropathy, and cognitive impairment. It delves into the underlying mechanisms, clinical manifestations, shared risk factors, diagnostic tools, management approaches, an extremely troublesome consequence of diabetes mellitus is diabetic neuropathy. It is linked to extreme morbidity, death, and a significant financial cost. The anatomical complexity of the brain has rendered it susceptible to a range of pathological illnesses, including T_2DM, and it has been shown that high blood sugar affects important brain regions involved in learning, memory, and spatial navigation. According to studies, patients with diabetes might have a cognitive loss that may go unnoticed for years. Furthermore, research on brain imaging suggests that hyperglycemia or a condition that co-occurs with T_2D has broad impacts on several brain areas in people with T_2D. Although the precise mechanism causing diabetes-related cognitive impairment is unclear, aberrant insulin function and decreased glucose metabolism are considered to play significant roles.

Keywords: Diabetes mellitus, neuropathy, cognitive impairment, insulin suppression

1. Introduction
The most common long-term diabetes consequences are diabetic neuropathies. This varied set of ailments impact many aspects of the neurological system and exhibit a range of clinical presentations. For a variety of reasons, it's crucial that diabetic patients with neuropathy are promptly diagnosed and treated appropriately. The diagnosis of diabetic neuropathy is one of exclusion. Patients with diabetes may experience non-diabetic neuropathies, which may be managed with certain therapies. Diabetes mellitus is a long-term metabolic condition that affects several organ systems, including the brain and neurological system, and is determined by hyperglycemia. considerable medical and social issue today is diabetes mellitus, which affects over 350 million individuals globally (Sims-Robinson C *et al*., 2015) [50]. Significant concerns for national health care systems is improved prevention and treatment of it. however, T_1DM and intellectual disability have received significantly less attention. Diabetes-related cognitive impairment has grown to be a significant drain on the available healthcare resources repercussion of rising T_2DM prevalence and longer life expectancy. (Kim B *et al*., 2015) [49].
T_2DM has an impact on a number of bodily organs, including the brain. There is little understanding of and research on the link between T_2DM and cognitive deterioration. Although the precise cause of intellectual disability in diabetes is unclear, it is frequently linked to aberrant insulin action and poor glucose metabolism. In addition, long-term hyperglycemia damages neurons and produces progressive glycation final products that cause oxidative stress and neuronal impairment. Other significant variables that might result in neuronal injury and cognitive impairment are dyslipidemia and inflammation (Naguib *et al*., 2020) [44].
T_2DM is strongly associated with dysfunctional performance across a range of intellectual spheres and also abnormalities in brain structure (Mirahmadizadeh *et al*., 2020) [3]. T_2DM and the associated cognitive impairment can significantly reduce a person's quality of life at any age (Abdellatif *et al*., 2020; Xia *et al*., 2020) [1, 49]. According to Sharma *et al*. (2020) [17] and Srikanth *et al*. (2020) [53], diabetic individuals are less able to withstand fatigue and retain cells that are more activated by inflammatory pathways. According to some reports, hyperglycemia increases the chance that brain blood vessels will be harmed.

2. Impairment of intellectual function in diabetes

Cognitive impairment and diabetes evidence of prospective and cross-sectional relationships between type 2 DM and moderate cognitive impairment, memory, and executive functioning was discovered in reviews of epidemiological studies of cognitive impairment in individuals with DM (Pasquier *et al*., 2006) [41]. Validated techniques for the identification of cognitive impairments may also be applied to patients with DM (Pasquier *et al*., 1999) [42].

This is probably because Alzheimer's disease and vascular dementia are more common (Cukierman-Yaffee T., 2009*)* [9]. Histopathological, molecular, and metabolic anomalies are typical of Alzheimer's disease. There is currently a rapid expansion of literature that links insulin deficiency and insulin resistance to Alzheimer's disease-like neurodegeneration, but this flood of fresh data is rife with conflicting and unresolved ideas about the potential roles of type 2 diabetes, the metabolic syndrome, and obesity in the pathogenesis of the disease.

Encephalopathies caused by diabetes are increasingly recognised as DM consequences. Regarding the underlying processes and the nature of the cognitive deficits that ensue, T_1DM and T_2DM appear to be different from one another. Epidemiological studies show that people with diabetes, particularly type 2 diabetes, are more likely to develop dementia and cognitive impairment (Reijmer YD *et al*., 2010) [46]. Hypo- and hyperglycemia, vascular risk factors, micro- and macrovascular problems, depression, and hereditary factors are only a few examples of potential risk factors.

T_2DM is linked to mild cognitive declines in non-dementia individuals that progress gradually over time, as well as an elevated risk of more severe cognitive decline and dementia. Between these two "types" of cognitive impairment, there appears to be a difference in the age groups and stages of development that they affect. In light of this, it has been hypothesised that the moderate and severe cognitive deficits seen in type 2 DM patients reflect distinct processes, presumably with discrete risk factors and aetiologies (Reijmer YD *et al*., 2010) [46]. In any case, dementia and cognitive decline both put a significant burden on patients and their loved ones, therefore any ways to stop these age-related changes should be taken into account. The majority of type 2 DM cognitive impairment investigations have been conducted on adults or the elderly (Reijmer YD *et al*., 2010) [46]. In comparison to obese teenage controls, a new preliminary investigation incorporating MRI In the absence of clinically significant vascular illness, these aberrations may be the consequence of a combination of minor vascular alterations, abnormalities in glucose and lipid metabolism, and small variances in adiposity.

3. Mechanism hyperglycemia-induced cognitive impairment

Numerous interrelated pathways have an impact on how diabetic neuropathy and cognitive impairment proceed. Oxidative stress, inflammation, and microvascular damage brought on by chronic hyper-glycemia have an adverse effect on the health of neurons and cognitive performance. Glucose serves as the primary energy source with its roots of soma (Howarth *et al*., 2012; Fioramonti and Pénicaud, 2019) [4, 15]. Even though it only makes up 2% of physical property, the brain uses more than 20% of daily energy intake (Erbsloh *et al*., 1958) [14]. Since neurons are always working to regulate important physical functions necessary for survival, they need double the efficiency of other body cells (Harris *et al*., 2012; Mergenthaler *et al*., 2013) [21, 43]. Neurons also function during sleep to regulate the circadian rhythm besides performing other essential jobs. The normal functioning of the brain's metabolic processes, vitality, cerebral signalling, cognitive function, neurotransmission, and synaptic plasticity all depend on persistent blood sugar. Although the brain relies on glucose substantially, severe and chronic hyperglycemia may be dangerous (Heni *et al*., 2015) [38].

The brain is one of several bodily organs that are impacted by T_2DM. It is poorly understood and rarely discussed how T_2DM and cognitive deterioration are related. However, decreased glucose metabolism and aberrant insulin action are frequently linked to cognitive impairment, even if the precise mechanism behind cognitive impairment in diabetes is unclear. According to studies Hazari *et al*., (2015) [34]; Rama and Sagar, (2019) [45] dyslipidaemia, inflammation, and alterations in the hypothalamic-pituitary-adrenocortical axis are all caused by hyper-glycemia. Chronic hyperglycemia is also harmful to neurons and causes advanced glycation end products, which cause oxidative stress and neuronal impairment. The other significant variables that might harm neurons and affect cognition include dyslipidemia and inflammation (Naguib *et al*., 2020) [44].

According to Mirahmadizadeh *et al*. (2020) [3]; and Dove *et al*. (2021) [2], T_2DM is strongly associated with both aberrant brain structure and subpar performance in several cognitive areas. According to Abdellatif *et al*. (2020) [1] and Xia *et al*. (2020) [49], T_2DM and the associated cognitive impairment can significantly lower people's quality of life. According to Sharma *et al*. (2020) [17] and Srikanth *et al*. (2020) [53], Patients with diabetes have cells that are more stimulated by inflammatory pathways and have a lower ability to endure oxidative damage.

Hyperglycemia has reportedly been linked to a dangerous impact of brain blood vessel injury. Hippocampal damage, a decrease in grey matter density, and a shift to the white matter microstructure are the structural alterations seen in the diabetic brain.

4. Cognitive decline when diabetes associated

Mechanisms behind the cognitive deterioration brought on by diabetes. Numerous metabolic pathways, including the polyol route, Abnormally, high blood glucose levels can activate the protein kinase C (PKC) route, the hexosamine pathway, and the advanced glycation end products (AGE) system. and this can result in neuronal damage. A mechanism by which hyperglycemia impairs cognitive function. Hyperglycaemia causes synaptic failure, oxidative damage IR, neuroinflammation, mitochondrial dysfunction, vascular damage, BBB disruption, elevated oxidative stress and neuronal injury

4.1 Role of hyperglycemia and hypoglycemia

Chronic hyperglycemia may set off processes that lead to endothelial dysfunction and neuronal injury, which together may eventually cause cognitive impairment (Strachan MW *et al*., 2010) [52].

In the work by Glaser *et al*. (2012) [18] and Glaser N *et al*. (2012) [18], adolescent rats with STZ-induced T_1DM were used as an animal model to see if cognitive abnormalities (decreased memory) could be found following a single episode of diabetic ketoacidosis. It is becoming more and more clear that hypo-glycemia raises the risk of

cardiovascular disease.
In older individuals, the link between hypoglycemia and cognitive impairment may become obvious. However severe hypoglycemia (Jacobson AM *et al*., 2011) [22] was not linked to a long-term deterioration in cognitive function in young patients.

4.2 Hyperglycemia's effect on brain structure
According to Vieira *et al*. (2018) [35], and Biessel's and Whitmer, (2020) [16], hyperglycemia can injure brain nerves and increase the chance of mental disability. The anatomical deformity in the brain linked to T_2DM includes alterations to both the grey and white matter (Chen *et al*., 2021) [54]. Cognitive deterioration and structural brain abnormalities, particularly in the hippocampus, are seen in T_2DM patients (Li *et al*., 2020) [39]. Reduced total and localised white and grey matter volumes in patients with T_2DM are indicative of brain shrinkage (Moran *et al*., 2013) [7]. White matter hyperintensities were also shown to be somewhat more prevalent in T_2DM patients' brains than in non-T_2DM individuals (Moran *et al*., 2017) [6]. These brain abnormalities might act as visualizing any life signs for T_2DM by itself or in combination with intellectual decrease (Zhang *et al*., 2011) [25].
Adults with T_2DM are somewhat more prone to develop diabetes than people without it global brain shrinkage, which develops gradually over time in contrast to normal ageing (Knopman *et al*., 2005; Knopman, *et al*., 2011) [11, 10]. The prevalence of vascular lesions is also increasing particularly lacunar infarcts. Numerous studies looked at the connection between the shrinking of the cortex or the subcortex or both and brain atrophy brought on by diabetes. Hippocampal atrophy may develop in T_2DM patients, according to certain views. Numerous studies have suggested that the medial temporal lobe's hippocampus, in particular, atrophy as an indication of neuro-degenerative (Brundel *et al*., 2014) [33].

4.3 Oxidative stress
It has been established that oxidative stress has a role in both the development and complications of diabetes. Additionally, there is evidence linking hyper-glycemia to a decrease in flavonoid levels in the brain. (Valko *et al*., 2007) [37]. According to studies by Fukui *et al*. (2002) [28] and Comin *et al*. (2010) [12], elevated oxidative stress in diabetic rats has been associated with the emergence of cognitive impairments. In their study, La Sala *et al* (2016) [30] on Circulating miR-21 and glycaemic dysfunctions are related, according to the molecular characterisation of impaired glucose tolerance (IGT) status. (La Sala *et al*., 2019) [31].
One of the main risk factors for AD is hyperglycemia (Li *et al*., 2017, Jash *et al*., 2020, Shieh *et al*., 2020;) [39, 26, 24]. Increased oxidative stress brought on by high blood sugar levels results in 4-hydroxynonenal (HNE), which weakens the antioxidant defence system in AD patients. The generation of may be enhanced in AD patients due to elevated amounts of HNE in the blood and brain (Arimon *et al*., 2015; Di Domenico *et al*., 2017; Liou *et al*., 2019) [40, 13, 8]. This may be due to related autoantibodies neutralising HNE adducts and A, as demonstrated by Sanotra *et al*. (2022) [36] The depletion of these essential neutralising antibodies and the promotion of a cellular milieu for neurodegeneration that results in pathologic conditions like AD may occur when levels of HNE adducts and A keep increasing (Sanotra *et al*., 2022) [36]. Everyone is aware that increased levels of protein kinase C isoform activation, increased flux through the polyol pathway, and increased flux through the hexosamine pathway all contribute to hyper-glycemia-induced neurotoxicity, which worsens damage from free radicals and vascular problems (Brownlee, 2001) [32].

5. Activity of insulin suppressed
Despite the fact that the brain is an organ that does not require insulin, insulin may cross the blood-brain barrier and bind to acceptors on glial cells and neurons. Although it is uncertain if the CNS exhibits insulin resistance, new research has suggested that the advancement of adiposity and T_2DM may be influenced by insulin sensitivity. Insulin, which has a variety of roles in the brain, increases glucose uptake in the frontal lobes and hippocampus, two of the key areas involved in memory regulation. Insulin strengthens the synapses that link brain cells, assisting in the creation of new memories. The neurotransmitter acetylcholine is essential for cognition, and insulin controls how it is metabolised and released. Finally, according to, to Arnold *et al*. (2018) [51], insulin helps blood vessels grow.
According to Young *et al*. (2006) [48], insulin causes high levels in the IDE (insulin-degrading enzymes) and causes the release of the amyloid peptide outside of cells. Lack of insulin causes to accumulate hyperinsulinemia resistance, there is a decrease in insulin receptors and insulin in the brain. (Kawamura, *et al*., 2012) [27]. High insulin levels stimulate IDE consumption because IDE destroys insulin, which increases the amount of A deposition. Cognitive impairment happens as a repercussion high level of accumulation (Craft, 2005; Kodl and Seaquist, 2008) [47, 5].

6. Brain Insulin Resistance
The body's reduced sensitivity to insulin is the hallmark of insulin resistance (Goldstein, 2002) [19]. Brain cells that are insulin resistant do not react to insulin. The insulin receptor's downregulation, inefficiency to grid insulin, or inappropriate activation of the insulin signalling cascade might enhance an absence of observance. The cellular level of this malfunction affects insulin homeostasis, inflammatory responses, and activities like brain glucose absorption in GLUT4-expressing neurons that are directly involved in insulin metabolism. Additionally, it influences neurotransmitter production, receptor modulation, and neuroplasticity.
Insulin and associated proteins are essential for brain cell viability. It appears that glucose and insulin control a number of brain functions, including memory and learning Persistently hypo and hyper-glycemia injure the brain and impair cognition through changing insulin activity. Recent studies indicate that liver insensitivity to insulin and central nervous system sensitivity to insulin are connected to the level of brain resistance to insulin and also fat muscle cells and tissue are connected. Affectation occurs in the brain areas related to learning, memory, and cognition. Long-term potentiation, a mechanism of cell-level memory formation, involves insulin.

7. Future Directions
Establishing causation and illuminating particular biochemical mechanisms between neuropathy and cognitive impairment should be the main goals of future studies. If proper neuropathy care can slow cognitive deterioration, longitudinal trials are required to confirm this. In the past ten years, much effort has been made to comprehend how

diabetes affects dementia and cognitive decline. Recent research has pinpointed the danger signs and potential causes of the cognitive impairment brought on by DM. Better treatments for cognitive complications of DM, such as AD, vascular dementia, and cognitive decline, may be created by using new developments in these processes. The effectiveness of TCM in treating DM-related cognitive deterioration has been demonstrated in several clinical investigations.

8. Conclusion

Further research is necessary to fully understand the complex link between neuropathy, cognitive impairment, and diabetes mellitus. The development of focused therapies to enhance outcomes for people with these illnesses can be guided by an understanding of the shared processes and risk factors. Patients with type 1 diabetes now have a much longer life expectancy because of advancements in medical technology. The higher risk of long-term diabetic issues is a natural result of longevity, though. As a result, there is growing interest in the clinical evaluation of intellectual ability and the standard of existence for all diabetic patients. Further research into this issue utilising cutting-edge neuroimaging techniques and biomarkers is necessary because the certainty of cognitive impairment both causes and greatly impairs the quality of life for diabetic patients.

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