

REVIEW ARTICLE

Type 2 diabetes mellitus-associated cognitive impairment and management

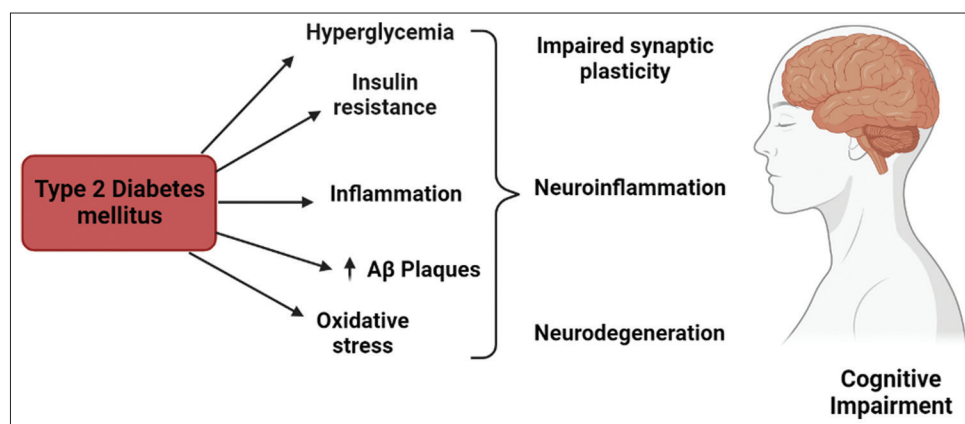
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ABSTRACT

Diabetes mellitus (DM) is a complex metabolic condition characterized by persistent hyperglycemia and poor metabolism due to insulin production irregularities and/or insulin resistance type 2 DM (T2DM) and dementia are linked through a variety of methods. Thus, in terms of the long-term repercussions of diabetes, the current idea focuses on cognitive damage, the exact pathophysiology of which is unknown. A new term, “diabetes-associated cognitive decline,” has recently been proposed to aid study in this field. This review discusses how different variables contribute to the development of T2DM. Furthermore, we investigated an expanding body of literature on insulin signaling in diabetics, as well as various factors such as insulin resistance, hyperglycemia, neuroinflammation, and A β (amyloid beta) plaques that may act alone or in combination to link T2DM with cognitive impairments. Finally, we looked at how physical activity and a balanced diet might help fight the condition.

KEY WORDS: Dementia, Diabetes mellitus, Hyperglycemia, Insulin resistance, Neuroinflammation



Graphical abstract: Various factors are responsible for diabetes-induced cognitive impairment. T2DM is caused by an increase in blood glucose levels over time. Furthermore, type 2 diabetes causes a variety of secondary problems, including cognitive impairment and an increase in inflammatory markers causing neuroinflammation, neurodegeneration, and synaptic plasticity impairment.

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INTRODUCTION

In the last few decades changes in lifestyle, especially related to overnutrition, physical inactivity, and aging have increased the global incidence of type 2 diabetes mellitus (T2DM).^[1] According to the International Diabetes Federation, currently, 387 million people have DM worldwide, and this number is expected to reach 592 million by 2035. T2DM is by far the most common form of diabetes, representing about 90–95% of DM cases.^[2] In older age people (>65 years), the prevalence of T2DM is 12–25% and is characterized by cell and tissue insulin resistance, metabolic dysregulation, and chronic inflammation. These clinical abnormalities have also been described in dementia cases. From the findings of various studies, the concept of disturbances in glucose metabolism and insulin resistance as underlying causes of neurodegeneration and dementia.^[3] More recently, epidemiological studies have provided further evidence for this link, where T2DM was shown to be associated with accelerated cognitive decline and increased risk of dementia (by 1.5- to 2-fold). Indeed, 10% of worldwide cases of dementia may be attributable to the metabolic disturbances associated with T2DM.^[4]

Hyperglycemia, or elevated blood sugar, is a symptom of type 2 diabetes brought on by insulin resistance. Cells that have developed insulin resistance stop responding to the hormone insulin, which controls cellular energy and metabolism.^[5] Years of type 2 diabetes may cause dementia for a variety of causes.^[6] One of them has to do with how diabetes affects the heart, and how the health of the heart affects the health of the brain. Both heart disease and high blood pressure are linked to strokes, which can result in dementia. Strokes, however, do not seem to be the exclusive cause of dementia, as some research revealed that diabetes increases the risk of dementia even after controlling for strokes.^[7] The idea that diabetes directly causes Alzheimer's disease (AD) is among the more fascinating ones. Due to the same molecular and cellular characteristics of diabetes and AD, AD has even been referred to as "type 3 diabetes."^[8] For instance, insulin is essential for the development of amyloid plaques and it also contributes to tau phosphorylation, which results in neurofibrillary tangles. In other words, whereas insulin resistance in the body can result in type 2 diabetes, it can also cause Alzheimer's/dementia disease-related plaques and tangles in the brain.^[3]

The population trends for dementia are very similar to those observed in DM. As a consequence, there is an increased co-occurrence of DM and dementia. We are now aware, however, that DM and dementia co-occur more frequently than is expected by chance alone. Epidemiological studies have established an increased risk of cognitive impairment among individuals with DM.^[9] DM is also linked to forms of cognitive dysfunction that are not as severe as dementia, such as mild cognitive impairment but also to even

more subtle cognitive changes, which are referred to as diabetes-associated cognitive decrements.^[10] The increased co-occurrence of DM with different types of cognitive dysfunction has important implications for patient management, particularly in older (over ~65 years of age) individuals in whom dementia and pre-dementia stages of cognitive impairment.^[11] Animal models of T2DM have reduced insulin transport to the brain, reduced insulin uptake, and reduced neuronal insulin, consistent with reported reduced insulin levels, insulin receptor expression, and insulin resistance in the brains of AD patients.^[3]

In this review, we discuss the various symptoms of cognitive dysfunction caused by DM. We focus on dementia/AD and the stages of cognitive impairment that precede dementia in T2DM, but we also talk about how prevalent dementia is globally. We refer to DM in general as "diabetes" throughout the paper and to the particular subtypes T1DM or T2DM as "T1DM" or "T2DM," respectively.

Prevalence of dementia worldwide

From the findings of numerous studies, nations around the world are dealing with a global epidemic of dementia, with low and rising rates of dementia beyond the age of 65. 65% of the share, or low-income middle-income countries (LMIC), are shared by them.^[12] The majority of Asia's countries (approximately two-thirds) are LMIC, where access to social protection, services, support, and care for those with dementia is relatively restricted. Asia currently has the biggest percentage of prevalent and incident dementia cases worldwide.^[13] Like many other LMICs, the Philippines is going through a demographic shift brought on by lifestyles and habits linked to industrial and economic development, like a rise in high-fat and sugary diets, sedentary habits, and tobacco use.^[14] Over the past three decades, the prevalence of obesity, hypertension, diabetes, and hypercholesterolemia has increased dramatically. These are well-known dementia risk factors that the nation has not appropriately addressed. The Filipino community can be regarded as having a high risk of dementia because of the high incidence of these particular risk factors. But in the Philippines, dementia is not seen as a significant public health issue.^[15]

Various studies demonstrated that, by 2040, 71.2% of all dementia patients are projected to reside in developing nations, up from the 60.1% who did so in 2001. Particularly in China, India, and Latin America, where dementia is quickly emerging as a major public health issue, the aging demographic transition is moving forward quickly.^[16] Despite the lack of epidemiological data on the incidence of dementia and its subcategories. According to the Delphi Consensus Study, dementia prevalence was higher in the Americas than in less developed parts of the world, like Africa and the Middle East. By 2040, the prevalence of dementia in Latin America will be comparable to that in North America.^[17] Japan has the lowest frequency of

dementia overall and AD specifically among developed nations. In addition, the frequency of dementia was very uniform throughout Eastern European nations.^[18]

An estimated 34 million Americans are thought to have type 2 diabetes, also known as adult-onset diabetes, which is a chronic condition. It can cause a variety of consequences, such as blindness, heart disease, and stroke if left untreated. In addition, there may be a link between diabetes and a higher risk of AD, according to researchers.^[19]

Impairment of insulin signaling and neurodegeneration

Insulin has many anabolic effects through a complicated signaling route that regulates cell metabolism, growth, and differentiation. The main characteristics of insulin-signaling pathways have been thoroughly detailed elsewhere.^[20] Under normal settings, insulin binding to IR activates a series of interconnected intracellular cascades, primarily the Ras/Raf/MEKK/MAPK and IRSs/phosphatidylinositol 3-kinase/protein kinase B pathways.^[21] Surprisingly, the latter is extensively implicated in the downstream signaling network that regulates protein synthesis, A β clearance, and glycogen synthase kinase-3 (GSK-3 β) activity. In turn,

GSK-3 β is required for tau phosphorylation, a soluble microtubule-binding protein whose physiological activity stabilizes microtubules in axons and contributes to neuronal growth, neuronal survival, synaptic plasticity, and learning memory.^[22] Although insulin increases glucose uptake into muscles and adipose tissues while inhibiting hepatic gluconeogenesis during the fed state, insulin is essential for neuronal survival, synaptic plasticity, and function in the brain.^[23] Once considered an insulin-insensitive organ, the brain is currently recognized as a target for insulin action, and the IR density is particularly high in regions of the CNS such as the hippocampus, involved in memory, the hypothalamus, critical for metabolic control, as well as in other areas including the olfactory bulb, cerebellum, amygdala, and cerebral cortex.^[24] Once thought to be an insulin-insensitive organ, the brain is now recognized as a target for insulin action, with IR density particularly high in areas of the CNS such as the hippocampus, which is involved in memory, the hypothalamus, which is important for metabolic control, and other areas such as the olfactory bulb, cerebellum, amygdala, and cerebral cortex [Figure 1].^[25]

GSK-3 β and tau phosphorylation

GSK-3's function was initially assumed to be the phosphorylation of just GS, which inactivated GS.

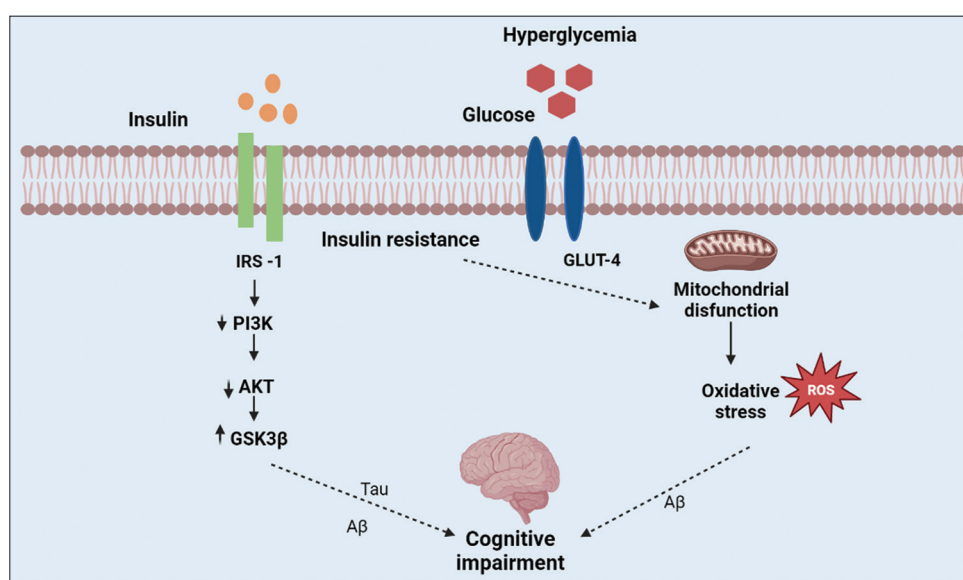


Figure 1: Proposed mechanisms of cognitive impairment associated with T2DM

The main factor causing insulin resistance in the brains of people with Alzheimer and disease is elevated levels of oxidative stress. By downregulating insulin receptors (IR) at the blood–brain barrier and resulting in reduced insulin transport into the brain (as seen in AD), persistently high levels of circulating insulin (as seen in the first phase of T2DM) may have a negative impact on memory and other cognitive functions. This condition is known as insulin resistance. From a biochemical perspective, the absence of interaction between insulin and IR is linked to an increase in the inhibitory phosphorylation on the substrate of the insulin receptor. Here, the main mechanism by which the insulin-signaling pathway is deactivated in cases of insulin resistance is serine phosphorylation of the insulin receptor component. By blocking the translocation of glucose transporter 4, this reduces glucose absorption by inactivating the phosphatidylinositol 3-kinase/protein kinase B signaling cascade. In addition, the activation of glycogen synthase kinase 3 results in the overexpression of A β proteins and the hyperphosphorylation of tau proteins. Oxidative stress can be brought on by conditions such as insulin resistance, and mitochondrial dysfunction, which in turn can promote an increase in the production of A β .

However, subsequent research has revealed that GSK-3 can also phosphorylate tau protein. Mammalian GSK-3 subtypes include GSK-3 α and GSK-3 β , the latter of which is important in tau protein phosphorylation.^[26] Excessive GSK-3 β activation promotes aberrant hyperphosphorylation of tau protein, aggravates neurodegeneration, interferes with normal synaptic plasticity, and accelerates the pathology process in AD patients. GSK-3 β is crucial in the pathogenic alterations of tau protein in AD.^[27] Huat *et al.* discovered that co-expression of GSK-3 β reduced axonal dilatation and lesions in the CNS of tau-transgenic mice. A decrease in this kinase activity restricts the growth of motile mitochondria, which regulates mitochondrial axonal transport.^[27] As a result, tau phosphorylation by GSK-3 β may be important for axonal elongation during development; in addition, GSK-3 β phosphorylates the tau protein at several locations in intact cells.^[28] Furthermore, GSK-3 β mediated phosphorylation of Ser404 protects the *Drosophila* visual system, and studies have shown that phosphorylation-incompetent tau protein is more dangerous for synaptic damage than hyperphosphorylated tau protein, and surprisingly, phosphorylation can extend *Drosophila* longevity.^[28] Lars Ittner *et al.* proposed in a paper published in *Science* that tau phosphorylation is to protect neurons from harm.^[29] The protein aids in the protective phosphorylation of tau and interferes with the neurotoxic complex formed by A β in the early stages of the disease, and they suggest that tau protein phosphorylation initially has a protective effect on neurons, but A β can attack the protective function until the function is gradually lost.^[30] At this point, the level of toxicity will cause neuronal death and cognitive impairment associated with AD. Tau phosphorylation is vital in the brain and may be a key mechanism of repair and damage resistance, although tau hyperphosphorylation is also important. In AD, it is critical to keep tau phosphorylation within an acceptable range through controlling the GSK-3 β signaling pathway.^[31]

Management

Role of exercise and diet

The synchronization of breathing and movement is a key component of yoga asanas, which highlight the connection between the body, mind, and consciousness.^[32] They entail relaxing and doing stretches or twists. The secret to completing a yoga posture well is to do so comfortably and steadily. Based on overall well-being and mind-body treatment, yoga positions for diabetes control and cognitive impairment receive good marks.^[33] Exercise has been shown to help people lose weight and change their lifestyles. However, yoga has been successfully used to treat metabolic abnormalities and on a physiological level. Several studies have shown that yoga is more effective in diabetes control than endurance exercise.^[34] Yoga can reduce anxiety and stress, obesity, and associated oxidative stress. It thereby regulates diabetes-induced cognitive decline.

An additional healthy behavior that persons practiced was linked to an 11% lower incidence of dementia. Medication use had no impact on the relationship between healthy lifestyle score and dementia risk.^[35] We should eat in a way that will not cause excessive spikes in our blood sugar or insulin levels (low glycemic), that does not encourage inflammation, and that gives our bodies all the nutrients they require to achieve optimal brain health. According to a recent study, metabolites from healthier diets may contribute to the preservation of brain function in people of all racial and cultural backgrounds.^[36] Many metabolites, including lipids, amino acids, and steroids, have been associated with cognitive decline and dementia in the past. Diet is a significant source of many metabolites, which can be markers of various aspects of human health. What is already known about the connection between nutrition and cognition that what we eat can have an impact on our brain health has been further substantiated by new research from the Brigham and Women's Hospital researchers. According to the study, which was published in *Trusted Source in Alzheimer's and Dementia*, metabolites from healthier diets, such as the Mediterranean diet, were linked to improved cognitive performance, whereas metabolites from diets rich in sugar were linked to worse cognitive function.^[37] This kind of research demonstrates how our diet can have a significant impact on how our brains work. Diet affects more than just your weight; it also affects how your body and brain work and can have a big impact on your mental and physical health. Several (although not all, as discussed elsewhere in this appendix).^[38] Prospective studies have revealed a connection between dementia incidence and consumption of Trans or saturated fats. Saturated fat consumption is linked to a higher risk of cardiovascular illness and type 2 diabetes, which are linked to a higher risk of dementia [Table 1].^[39]

Anti-diabetic drug development in the treatment of cognitive impairment

For patients with T2DM, various anti-diabetic medications are available as monotherapies or in combination therapy. The majority of the medications are designed to treat neurological, cognitive, and cardiovascular clinical problems. Diabetes medications are categorized based on their mode of action. Several researchers looked into the clinical evaluation of anti-diabetic medicines in diabetic individuals with cognitive dysfunction.^[45] Sodium-glucose co-transporter 2 inhibits glucose reabsorption in the renal tubules. The efficacy of empagliflozin and dapagliflozin was studied in a mouse model.^[46] Plaque burden and neuronal inactivation have been found in treated mice. In another study, rats given dapagliflozin had better mitochondrial function and less cognitive impairment.^[47] Pioglitazone has been proven in triple-transgenic mice to alleviate cognitive impairment and diminish tau protein accumulation. In another experiment, pioglitazone was demonstrated to activate microglia. Treatment with pioglitazone also normalizes metabolic and circulatory

Table 1: Yoga asanas and their benefits in the management of cognitive impairment and holistic health improvement

Yoga Asanas	Yoga benefits/Health benefits	References
Surya namaskar/sun salutation	Stimulates insulin production through brain signaling. Significantly decreases hip circumference, exerting beneficial effects on glycemic outcomes. Rejuvenates pancreatic cells through the alternating abdominal contractions and relaxations involved in yoga practice. Improves blood supply to muscles. Enhances insulin receptor expression in the muscles, causing increased glucose uptake by muscles. Have positive effects on glucose utilization and fat redistribution in type 2 diabetes.	[40]
Shuddhi kriya /cleansing processes	Abdominal pressure created during exhalation	[40]
Kapalbhati (frontal brain purification)	Helps in the production of insulin and controlling glucose levels in the blood.	[41]
Anulom vilom (alternate nostril breathing)	Improves components of health-related fitness, that is, cardiorespiratory endurance, flexibility, and body fat percentage	[41]
Pranayama (regulated breathing)	Augment cerebral blood flow and oxygenation, improving neuronal activities in the brain centers, including those present in the limbic areas, hypothalamus, and medulla, and improve the sympathovagal outflow	[42]
Bhramari (humming bee breath)	Soothing and calming effect on the mind improves mental and physical health	[43]
Dhyan (meditation)	Beneficial psychological effects, such as faster reactions to stimuli and being less prone to various forms of stress reduction, anxiety reduction, and blood pressure control. Positive effects on sugar levels	[44]
Mindfulness	Better sleep, greater relaxation, more accepting approaches to illness and the illness experienced in people with diabetes and coronary heart disease	[44]

processes, lowers IR, and maintains reactive oxygen species in the hippocampus and cerebral cortex for learning and memory.^[48] Metformin is an oral hypoglycemic agent; numerous clinical studies on cognitive dysfunction in T2DM are being conducted. Metformin combined with sulfonyleureas has been shown to prevent dementia by up to 35%. Long-term metformin treatment has been associated with AD progression. Other medicines, such as thiazolidinedione, sulfonyleureas, or insulin, have not been linked to dementia or neurological problems.^[48] The medication employs aducanumab (Aduhelm), which was recently approved by the FDA for patients with moderate AD symptoms, such as those who can still do basic daily tasks independently. It reduced the protein deposits known as brain amyloid plaque, which are a fundamental feature of AD.^[49] Plaque reduction, on the other hand, has not been shown in trials to be a reliable predictor of cognitive performance. Other plaque-reducing medications have not shown significant patient benefit, and not everyone with plaques has or will develop AD.

CONCLUSION

Diabetes is a physiologic illness that can only be managed with medication and dietary changes. In this review, we talked about cognitive impairment caused by T2DM and the several T2DM pathologies that might induce cognitive impairment. This review article focuses on essential points that can aid future research on cognitive impairment associated with T2DM. Thus, both new and chronic cases

of DM should be evaluated for molecular abnormalities as well as neuroimaging for cognitive impairment. However, in developing nations, normal blood glucose levels are rarely routinely checked, posing a significant challenge to the health-care system. Insulin resistance inhibits the PI3K and AKT signaling cascades, as well as interaction with other pathways that accelerate cognitive decline and disrupt important memory regulators such as the GSK3 β cascade programs that target the treatment of patients with a cognitive impairment through early illness identification, combination treatments, lifestyle changes, and exercise programs have shown promising results on neuroprotection in pre-clinical and clinical studies.

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COMPETING INTERESTS' STATEMENT

None.

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