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A review of type 2 diabetes mellitus and cognitive impairment

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The association between type 2 diabetes mellitus (T2DM) and cognitive impairment represents a critical public health concern, particularly against the backdrop of the rising global prevalence of diabetes and aging populations. Accumulating evidence indicates that T2DM is linked to declines in multiple cognitive domains, which may progress to cognitive impairment or even dementia. This cognitive impairment arises from complex interactions among insulin resistance, chronic inflammatory responses, vascular injury and microangiopathy and oxidative stress. Clinical studies suggest that strict glycemic control combined with behavioral and lifestyle interventions may delay cognitive decline, though their long-term efficacy requires further evidence-based validation. Future research should leverage multi-omics technologies to identify early biomarkers for T2DM-related cognitive impairment, elucidate the underlying molecular mechanisms, identify specific therapeutic targets, and develop personalized intervention strategies. This review systematically examines the epidemiological correlations, pathophysiological mechanisms, and advances in clinical management of T2DM-related cognitive disorders, with the aim of providing a theoretical foundation for early prevention and targeted treatment.

1 Introduction

T2DM has emerged as a global epidemic and a major public health challenge. Global prevalence of T2DM is expected to increase to 7,079 cases per 100,000 population by 2030, reflecting a sustained upward trend across all regions (1). T2DM significantly elevates the risk of microvascular complications (e.g., retinopathy, nephropathy, neuropathy) and macrovascular diseases (e.g., coronary artery disease, stroke) (2). Cognitive impairment is defined as a decline in one or more cognitive domains, including memory, attention, orientation, judgment, and problem-solving abilities (3). Manifestations of impairment may include slowed information processing, memory deficits, and challenges in learning or

decision-making (4). Cognitive impairment severely impacts overall well-being by compromising social engagement and functional independence, increasing reliance on caregivers while reducing autonomy, and posing safety risks, ultimately elevating morbidity and mortality rates through diminished self-care capacity and delayed medical intervention (3, 5). Given the escalating global prevalence of T2DM and its profound implications for cognitive health, elucidating the underlying pathophysiological pathways and identifying preventive interventions are critical for mitigating dual disease burdens. Research in this domain holds significant clinical and societal relevance. Understanding how metabolic dysregulation accelerates neurodegenerative processes could inform early biomarkers for cognitive risk stratification and targeted therapies. Ultimately, advancing this field may enhance patient outcomes and quality of life.

2 Pathophysiology of T2DM and its impact on cognitive function

2.1 Basic pathogenesis of T2DM

T2DM is characterized by two central pathophysiological defects: pancreatic β-cell dysfunction and insulin resistance (IR). β-cell dysfunction manifests as inadequate insulin secretion or decompensation, ultimately resulting in hyperglycemia. IR refers to diminished responsiveness of peripheral tissues (e.g., skeletal muscle, adipose tissue, liver) to insulin signaling, glucose uptake into these cells becomes inefficient, resulting in its accumulation in the bloodstream and consequent hyperglycemia. To compensate, pancreatic β-cells augment insulin secretion, leading to a state of hyperinsulinemia. These defects mutually reinforce each other, establishing a vicious cycle. Chronic inflammation, ectopic lipid deposition, endoplasmic reticulum stress (ERS), and oxidative stress further exacerbate metabolic dysregulation by impairing insulin sensitivity and/or β-cell function, thereby driving the onset and progression of T2DM and its target organ damage (TOD) (6).

β-cells integrate signals from glucose, free fatty acids (FFA), hormones (e.g., incretins GLP-1/GIP), and neural inputs to dynamically regulate insulin secretion (7). Factors contributing to β-cell failure include: aging and genetic predisposition, incretin resistance/deficiency (e.g., impaired glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP] signaling), lipotoxicity (FFA-induced β-cell apoptosis) and glucotoxicity (chronic hyperglycemia-induced oxidative stress), insulin resistance-induced β-cell stress, islet amyloid deposition (excessive islet amyloid polypeptide [IAPP] aggregation), reactive oxygen species (ROS)-mediated damage and proinflammatory signaling (8).

IR is a multifactorial metabolic disorder marked by reduced responsiveness of insulin-target tissues (liver, adipose tissue, skeletal muscle) to physiological insulin levels. It is closely linked to metabolic syndrome (MS), where obesity, dyslipidemia, and hypertension amplify IR through: proinflammatory cytokine release (e.g., TNF-α, IL-6), ectopic lipid accumulation (hepatic and muscular lipotoxicity), oxidative stress-mediated inhibition of insulin receptor signaling (e.g., PI3K/Akt pathway) (9).

2.2 Impact of diabetes-related complications on cognitive function

2.2.1 Cerebrovascular complications

Diabetes-induced macrovascular pathologies, such as atherosclerosis (AS), drive structural alterations in cerebral vasculature, including stenosis, occlusion, and intima-media thickening—hallmarks of AS (10). Chronic vascular occlusion disrupts central hemodynamics, cerebral perfusion, and cerebrovascular function. Key functional impairments include: endothelial-dependent vasodilation deficits and impaired cerebrovascular autoregulation (11, 12). These dysfunctions directly manifest as abnormal cerebral blood flow (CBF) (13). Evidence linking carotid AS to cerebral atrophy suggests that sustained CBF reduction contributes to brain volume loss, a recognized precursor to vascular dementia (VD). Moreover, Chronic hypoperfusion exacerbates neuroinflammation by activating microglia, leading to white matter lesions (WMLs) and neurodegeneration. WMLs are strongly associated with progressive cognitive decline and eventual VD onset.

2.2.2 Diabetic retinopathy

Diabetic retinopathy, a microvascular complication of diabetes, may reflect systemic microvascular damage. Wu et al. reported that DR is associated with psychomotor slowing and attentional deficits. Electrophysiological studies in diabetic models demonstrate reduced neuronal activity in the primary visual cortex, impairing visual information processing (14). Meta-analytic evidence further links retinal pathology to cognitive decline, any retinopathy was significantly associated with the presence of dementia and cognitive deficits, as well as with reduced processing speed (15).These associations persist even in patients without overt retinopathy, suggesting that retinal microvascular changes (e.g., altered vessel caliber, fractal dimension) may serve as biomarkers of cerebral microangiopathy and neurodegeneration. Additionally, diabetes frequently induces visual system dysfunction, including impaired motion detection, reduced contrast sensitivity, and defective color discrimination, which may indirectly exacerbate cognitive load by disrupting sensory input integration (14).

2.2.3 Diabetic kidney disease

Diabetic kidney disease (DKD), a diabetes-specific complication characterized by progressive renal damage, exacerbates blood-brain barrier (BBB) disruption and is increasingly recognized as a risk factor for neurocognitive deficits. Clinical studies reveal a bidirectional relationship between renal dysfunction and cognitive impairment, where elevated urinary albumin excretion rate (UAER) predicts poorer cognitive performance, while declining glomerular filtration rate (GFR) is associated with worsening cognitive scores, highlighting a dose-dependent link between renal impairment and neurodegeneration (16). DKD contributes to cognitive impairment

through interconnected pathophysiological pathways. Impaired renal clearance of uremic toxins, such as indoxyl sulfate, promotes neuroinflammation and oxidative stress, accelerating BBB disruption and neuronal apoptosis (17). These mechanisms synergistically disrupt neurovascular homeostasis, creating a self-reinforcing cycle of neurodegeneration and cognitive decline in diabetic patients. Serum creatinine, an indicator of renal dysfunction, inversely correlates with cognitive performance in elderly diabetic populations, suggesting its potential as a prognostic marker for cognitive decline, while early detection of DKD through measures like UAER monitoring can help stratify dementia risk and guide interventions, such as renin-angiotensin system inhibitors, to preserve both renal and cognitive function (18).

2.2.4 Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN), a prevalent complication of diabetes, is increasingly linked to cognitive impairment. Evidence demonstrates that individuals with T2DM and DPN exhibit lower global cognitive performance compared to those without DPN, including deficits in memory, attention, and psychomotor speed (19). In type 1 diabetes, cognitive impairment is similarly pronounced, with DPN patients showing marked impairments in attention, visuospatial/executive functions, language, and abstract reasoning (20). Notably, painful DPN correlates with more severe cognitive deficits than painless DPN (21), particularly in domains of attention and memory. These findings suggest that DPN severity and subtype may serve as biomarkers for neurodegeneration risk in diabetic populations, underscoring the need for integrated neurological and cognitive assessments in diabetes care (22).

2.2.5 Diabetes-related foot complications

Emerging evidence highlights a significant association between diabetes-related foot complications (DRFC) and cognitive impairment. Studies demonstrate that individuals with DRFC exhibit more pronounced cognitive deficits compared to diabetic patients without foot complications, particularly in domains of verbal memory, executive function, and inhibitory control (23). Furthermore, diabetes-associated cognitive impairment encompasses broader deficits, including impairments in attention, memory, executive function, visuospatial abilities, and language. The severity of DRFC-related cognitive decline underscores the need for integrated care models addressing both metabolic and neurological health in diabetic populations (24).

3 Mechanistic insights into T2DM and cognitive impairment

3.1 Insulin resistance and cerebral metabolism

Insulin acts on insulin receptors in the brain to promote neurotransmitter synthesis, synaptic plasticity, and neuronal differentiation—processes critical for learning and memory. Insulin signaling in the brain is essential for normal cognitive function, particularly in key regions such as the hippocampus and prefrontal cortex (25), where it regulates glucose utilization, energy homeostasis, synaptogenesis and long-term potentiation (LTP). It also governs appetite regulation and systemic metabolic balance (26). Brain insulin resistance (BIR) is recognized as a key factor linking metabolic disorders like obesity and T2DM to cognitive decline. It disrupts normal insulin signaling pathways, leading to mitochondrial structural and functional abnormalities, which in turn result in impaired energy metabolism and increased oxidative stress. This dysfunction triggers neuronal damage and cognitive deterioration, ultimately contributing to cognitive impairment (27).

BIR reduces plasma levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (28), which plays a critical role in promoting structural and functional plasticity in the central nervous system (CNS) (29). Additionally, BIR downregulates the expression of neuronal glucose transporters (e.g., GLUT4), impairing cerebral glucose uptake (30). This energy deficit results in decreased brain glucose utilization, triggering neuronal metabolic dysfunction. Such metabolic disturbances not only compromise synaptic plasticity but may also threaten neuronal survival, contributing to memory deficits and executive dysfunction.

3.2 Chronic inflammatory response

Diabetes mellitus, a chronic metabolic disorder, significantly disrupts systemic and localized inflammatory responses, thereby compromising brain health. The systemic inflammation associated with diabetes promotes increased BBB permeability, neuroinflammation, and subsequent neurodegenerative alterations. These inflammatory processes are mechanistically linked to cognitive impairment and an elevated risk of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease.

Characterized by chronic low-grade inflammation, diabetes alters the expression of key inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and C-C motif chemokine receptor 2 (CCR2), which collectively modulate peripheral and central immune responses (31). Activation of inflammatory pathways, particularly those mediated by NF-κB, synergizes with oxidative stress and impaired autophagy to exacerbate neuronal damage and accelerate cognitive decline (32). Dysregulated inflammatory signaling in diabetic individuals amplifies ischemic brain injury.

3.3 Vascular injury and microangiopathy

Diabetes exerts profound detrimental effects on cerebrovascular health, precipitating vascular injury and microvascular pathologies closely associated with cognitive impairment. The relationship between diabetes and cerebrovascular pathology is multifaceted, encompassing both macrovascular and microvascular abnormalities that synergistically contribute to cognitive decline (33).

Accumulating evidence indicates that diabetes independently increases the incidence of cerebral infarctions and vascular brain injuries, both of which are critical determinants of cognitive deterioration (33). Diabetic-induced cerebrovascular damage manifests as endothelial dysfunction, increased arterial stiffness, and thickening of capillary basement membranes (34). These pathological alterations compromise cerebrovascular elasticity and integrity, leading to reduced cerebral blood flow and chronic cerebral hypoperfusion, thereby exacerbating cognitive deficits.

As an established risk factor for cerebrovascular diseases, diabetes is characterized by a higher prevalence of cerebral infarctions, white matter hyperintensities (WMH), and cerebral small vessel disease (CSVD) (33). These pathologies exhibit greater severity in diabetic populations and correlate with an elevated risk of accelerated cognitive decline. Preclinical studies utilizing diabetic rodent models demonstrate that hyperglycemia exacerbates cerebrovascular dysfunction, which parallels observed cognitive impairments, highlighting diabetes-specific vulnerabilities in neurovascular coupling (35).

3.4 Oxidative stress and neuronal injury

Chronic hyperglycemia drives oxidative stress, a pivotal mechanism underlying neuronal injury in diabetes. Sustained elevation of blood glucose promotes excessive generation of ROS and reactive nitrogen species (RNS), overwhelming endogenous antioxidant defenses. This redox imbalance critically contributes multifaceted biochemical cascades and cellular dysfunction. Prolonged hyperglycemia activates four major oxidative stress-inducing pathways: the polyol pathway, advanced glycation end-product (AGE) accumulation, protein kinase C (PKC) activation, and dysregulation of the hexosamine pathway (36, 37). These interconnected pathways work synergistically to amplify ROS production, which directly damages neuronal membranes, proteins, and DNA.

Moreover, oxidative stress activates redox-sensitive transcription factors, such as NF-κB, leading to the upregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) (37, 38). These cytokines exacerbate neuroinflammation, creating a vicious cycle in which oxidative stress and inflammation synergistically drive neurodegeneration. Diabetic rodents exhibit elevated oxidative markers (8-OHdG, nitrotyrosine) and increased apoptosis in dorsal root ganglion (DRG) neurons, confirming oxidative damage as a driver of peripheral neuropathy (39).

3.5 The interplay between T2DM and Alzheimer's disease

Emerging evidence reveals significant pathophysiological intersections between diabetes mellitus, particularly T2DM, and neurodegenerative disorders, with Alzheimer's disease (AD) demonstrating particularly strong associations (40). T2DM has been established as an independent risk factor for accelerated cognitive decline and neurodegeneration, potentially increasing AD susceptibility through shared biological mechanisms. The disease continuum appears driven by overlapping pathways including chronic insulin resistance, systemic inflammation, and mitochondrial dysfunction, which collectively create a neurodegenerative milieu (41, 42). Notably, hallmark AD pathologies – β-amyloid (Aβ) plaque deposition and tau protein hyperphosphorylation – are exacerbated by diabetic metabolic disturbances. Sustained hyperglycemia and impaired insulin signaling in T2DM patients potentiate amyloidogenic processing while compromising tau protein homeostasis, thereby accelerating the neuropathological cascade characteristic of AD progression (43).

3.6 T2DM-related cognitive impairment and gut-brain axis disruption

The gut-brain axis is a bidirectional communication system between the gastrointestinal tract and the central nervous system that influences cognitive function through various mechanisms (44). In T2DM, significant alterations occur in the composition of the gut microbiota, which affect cognitive abilities. Specific genera (e.g., *Parabacteroides* and *Lactobacillus*) have been shown to modulate metabolites, thereby improving cognitive behavior in diabetic models (45). Changes in the gut microbiome directly or indirectly impact brain function through vagal, endocrine, and immune pathways. Metabolites directly activate vagal afferent nerves, transmitting signals to the brain via vagal pathways. In the endocrine pathway, enteroendocrine L cells release gut hormones such as GLP1, peptide YY (PYY), and cholecystokinin (CCK), which subsequently influence learning, memory, and mood. Within the immune pathway, immune cells including helper T cell 1 (Th1), helper T cell 17 (Th17), regulatory T cells (Treg), neutrophils, and macrophages are stimulated (46). Fecal microbiota transplantation has demonstrated potential in alleviating diabetes-related cognitive decline by altering gut microbiota composition and enhancing brain insulin signaling pathways (45).

Although the gut-brain axis plays a significant role in T2DM-related cognitive impairment, it is essential to consider other contributing factors, such as genetic predisposition and lifestyle. The interactions between these factors and the gut-brain axis are complex and require further research to fully elucidate the underlying mechanisms.

4 Sociodemographic moderators in T2DM-related cognitive impairment

In recent years, an increasing number of studies have explored the potential roles of gender, age, educational level, and social determinants in the link between T2DM and cognitive function from demographic and sociological perspectives, offering new pathways for identifying vulnerable populations and developing intervention strategies.

Age is a key factor for cognitive impairment in T2DM patients. Older age has consistently been associated with a higher risk of cognitive impairment. Studies show that individuals aged 60 and above with T2DM are particularly susceptible to cognitive decline, with the risk increasing with advancing age (47, 48).

Research shows that, independent of diabetes status, women generally perform better in certain cognitive domains (e.g., global cognition and verbal abilities) (49). However, other studies suggest that middle-aged men with T2D have a higher risk of mild cognitive impairment (MCI) compared to women (50).

Education is widely recognized as a core component of cognitive reserve and also plays a significant moderating role in the association between T2DM and cognitive function. Research by Reinke published in *BMC Public Health* indicates that higher education is not only associated with better glycemic control but can also slow diabetes-related cognitive decline (51). Peña-González further points out that education can mitigate the negative effects of the disease by building cognitive reserve, enhancing an individual's neuroplasticity and cognitive resilience in the face of hyperglycemia or metabolic dysregulation (52).

Social determinants such as socioeconomic status, race/ethnicity, and healthcare access also play crucial roles in T2DM-related cognitive impairment (53). Studies comparing elderly populations in the US and Mexico found that low socioeconomic status is significantly associated with cognitive decline, and the level of social support significantly influences the cognitive trajectory of diabetes (54).

In summary, gender, age, education, and social determinants all play complex and interacting roles in the link between T2DM and cognitive function. Research indicates that individuals with early-onset diabetes, those with lower educational attainment, and those of low socioeconomic status face a higher risk of cognitive impairment. Theories such as cognitive reserve, the accumulated stress model, and research on health inequalities provide multidimensional perspectives for understanding diabetes-induced cognitive impairment. Future research should deepen efforts in the following areas: First, strengthen stratified studies on different population subgroups to precisely identify high-risk groups. Second, integrate metabolic, physiological, psychological, and social dimensions to construct multi-level assessment models. Third, enhance educational interventions and social support within community health promotion to mitigate the cognitive risks stemming from structural health inequalities.

5 T2DM management and cognitive impairment

5.1 Glycemic control and cognitive function in T2DM

The relationship between glycemic control and cognitive performance represents a critical focus in diabetes research, particularly in the context of neurodegeneration. Accumulating evidence indicates that suboptimal glycemic management is strongly associated with accelerated cognitive impairment, whereas rigorous blood glucose regulation may attenuate neurodegenerative progression. In patients with T2DM, chronic hyperglycemia and elevated glycated hemoglobin (HbA1c) levels correlate with measurable declines in global cognitive function. Multiple studies have shown that improving blood sugar control can enhance cognitive function. For example, a systematic review found that antidiabetic treatment can significantly alleviate the decline in cognitive ability in diabetic patients (55).

5.2 Potential effects of common glucose-lowering drugs on cognitive function

The potential impact of glucose-lowering drugs on cognitive function is multifaceted, encompassing both adverse effects resulting from drug-induced hypoglycemia and possible cognitive benefits associated with specific drugs. These effects are systematically summarized in Table 1.

As a first-line oral hypoglycemic agent for T2DM, metformin demonstrates bidirectional regulatory effects on cognition. Accumulating evidence suggests its neuroprotective properties through mechanisms including AMPK signaling pathway activation and oxidative stress inhibition, with demonstrated improvements in specific cognitive domains such as verbal learning, working memory, and executive function in diabetic patients (56). Notably, prolonged metformin therapy may induce vitamin B12 deficiency, which has been established as a risk factor for cognitive decline (57, 58). This dual mechanism indicates that while metformin may mitigate diabetes-related neurodegenerative processes, it could paradoxically impair cognitive health in susceptible individuals through nutritional metabolic disturbances. Clinical protocols should therefore incorporate regular serum vitamin B12 monitoring and timely nutritional supplementation to prevent associated complications (59).

5.2.1 GLP-1 receptor agonists

The neuroprotective effects of GLP-1RA are believed to be mediated through multiple mechanisms, including the reduction of neuroinflammation, enhancement of mitochondrial function, antioxidant stress, prevention of β-amyloid and tau protein aggregation, and improvement of synaptic function (60). A systematic review and meta-analysis found that GLP-1RA did not significantly affect overall cognitive function in patients with type 2 diabetes. However, subgroup analysis indicated potential benefits for patients under 65 years of age or those without a history of cardiovascular or cerebrovascular disease, suggesting that age and comorbidities may influence cognitive outcomes with GLP-1 therapy (61). Another study reported that the GLP-1RA liraglutide improved short-term memory and memory composite scores in obese patients with prediabetes or early-stage type 2 diabetes, independent of weight loss effects. This suggests that GLP-1RA provide direct cognitive benefits in early-stage diabetes (62). In animal models, GLP-1RA have shown promising results in improving cognitive function. For example, liraglutide improved

memory retention and increased hippocampal neuron count in an Alzheimer's disease mouse model, indicating its potential neuroprotective effects (63).

5.2.2 Sodium-glucose cotransporter 2 inhibitors

(SGLT2is) exerts beneficial effects on cognitive impairment through multifaceted mechanisms involving metabolic regulation, anti-inflammatory actions, antioxidant properties, and modulation of neurotrophic factors (64). Preclinical studies demonstrate that dapagliflozin ameliorates cognitive deficits in diabetic murine models by restoring hippocampal mitochondrial dynamics - a critical process for synaptic plasticity and memory formation (65). Particularly in dual pathology models combining T2DM and AD, SGLT2is not only enhance insulin sensitivity but also significantly reduce β-amyloid deposition, addressing two fundamental pathological hallmarks of AD.

Clinical investigations reveal substantial cognitive improvements associated with SGLT2i therapy, especially in populations with mild cognitive impairment or established dementia. A meta-analysis quantifying cognitive outcomes showed a standardized mean difference of 0.88 (95% CI: 0.32-1.44) in cognitive assessment scores, indicating clinically meaningful enhancement (66).

Notably, large-scale clinical data analysis demonstrates significant dementia risk reduction with SGLT2i use. In a population-based study of 331,908 T2DM patients, SGLT2i treatment was associated with 23% lower dementia incidence (HR: 0.77; 95% CI: 0.71-0.84) (67). The observed cerebroprotection may derive from synergistic effects including blood pressure optimization, sodium homeostasis regulation, and metabolic reprogramming, collectively preserving neuronal integrity in chronic metabolic disorders (68).

5.2.3 DPP-4 inhibitors

DPP-4is improve glucose tolerance and insulin sensitivity, which are critical for maintaining cognitive function in diabetic patients. Improvements in metabolic parameters such as reduced fasting blood glucose and HbA1c levels are consistently associated with better cognitive outcomes (69, 70). Sitagliptin has been shown to reduce oxidative stress and promote hippocampal neurogenesis, both essential for cognitive health. These effects are further supported by the upregulation of genes involved in neuroprotection and synaptic plasticity (69).

At the molecular level, DPP-4is likely exert their benefits via the AMPK/mTOR pathway, enhancing neuronal autophagy and reducing tau protein phosphorylation—mechanisms that are neuroprotective (71). A meta-analysis involving 5,583 participants demonstrated that DPP-4is significantly reduce the incidence of cognitive impairment in T2DM patients, with a standardized mean difference (SMD) of 0.99. Additionally, clinical studies revealed that these agents improve scores on the Mini-Mental State Examination (MMSE) and Instrumental Activities of Daily Living (IADL), indicating measurable cognitive benefits (70, 72). Notably, in elderly patients with mild cognitive impairment, DPP-4is stabilize cognitive function by reducing glycemic variability (73).

Preclinical evidence further supports these findings: in insulin-resistant rat models, DPP-4is such as sitagliptin and vildagliptin improve cognitive behaviors and restore cerebral mitochondrial function, demonstrating protective effects against diet-induced cognitive decline (74).

5.2.4 Sulfonylureas

Sulfonylureas may exert dual effects on cognitive function in diabetic populations. Preclinical studies indicate potential neuroprotective properties: glimepiride ameliorated learning and memory deficits in diabetic rodent models, potentially through antioxidant mechanisms and upregulation of BDNF levels (75). Similarly, glyburide prevented chronic stress-induced cognitive impairment in murine models, possibly via modulation of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor stabilization (76).

However, these potential benefits must be weighed against well-documented adverse effects. Sulfonylureas are associated with hypoglycemia episodes and progressive β-cell exhaustion, factors that may exacerbate cognitive decline, particularly in elderly patients with compromised cerebral autoregulation. Population-based studies reveal concerning epidemiological patterns. A retrospective cohort analysis (n = 45,632 T2DM patients) comparing sulfonylureas with DPP-4is demonstrated increased dementia risk with sulfonylurea use over 4.82 mean follow-up years (77). Network meta-analyses further position sulfonylureas as second-highest among antidiabetic agents for dementia risk escalation (surface under cumulative ranking [SUCRA] score: 73.4), surpassed only by insulin analogs (78).

5.3 Behavioral and lifestyle interventions: synergistic effects of diet, exercise, and cognitive training

Accumulating evidence supports behavioral and lifestyle interventions—including dietary modification, physical exercise, and cognitive training—as promising non-pharmacological strategies to mitigate diabetes-related cognitive decline. T2DM is a well-established independent risk factor for mild cognitive impairment and dementia progression. While current pharmacological interventions remain suboptimal, multimodal lifestyle approaches demonstrate clinically meaningful potential for preserving neurocognitive function in T2DM populations.

5.3.1 Exercise and cognitive function

Controlled trials reveal differential cognitive benefits of structured exercise regimens in T2DM patients. Both resistance training and aerobic exercise protocols show efficacy (79), with meta-analytic data indicating significant attenuation of cognitive decline through multicomponent programs (sessions >40 minutes, ≥4 times weekly over 6 months; pooled effect size: 0.61, 95% CI: 0.40–0.82) (80). Notably, intervention heterogeneity exists, with some studies reporting only moderate effects or null findings in

TABLE 1 Potential effects of common glucose-lowering drugs on cognitive function.

Medicine	Glucose-lowering efficacy	Core mechanisms of glucose lowering	Cognitive outcomes
Metformin	High	Suppression of hepatic gluconeogenesis and improvement of peripheral insulin sensitivity	Activation of AMP-activated protein kinase (AMPK) signaling and Attenuation of oxidative stress
GLP-1RA	High to very high	Stimulation of insulin secretion and Suppression of glucagon secretion	Reduction of neuroinflammation, enhancement of mitochondrial function, antioxidant stress, prevention of β-amyloid and tau protein aggregation, and improvement of synaptic function
SGLT2is	Intermediate to high	Inhibition of renal glucose reabsorption	Anti-inflammatory actions, antioxidant properties, and modulation of neurotrophic factors
DPP-4i	Intermediate	Inhibition of dipeptidyl peptidase-4 (DPP-4) activity and Enhancement of intact GLP-1 and GIP levels	Activation of AMPK signaling cascade and attenuation of tau protein phosphorylation
Sulfonylureas	High	Potentiation of pancreatic β-cell insulin secretion	Antioxidant stress and promotion of BDNF transcription

single-modality approaches, underscoring the need for optimized intensity-duration parameters (81, 82).

5.3.2 Cognitive training interventions

Domain-specific cognitive interventions yield measurable neuropsychological improvements. Dual-task training and targeted cognitive remediation significantly enhance memory performance and executive function in T2DM cohorts. Although mechanistic links to glycemic control remain inconclusive, these interventions demonstrate synergistic benefits when combined with lifestyle education, enhancing both cognitive capacity and diabetes self-management skills (83).

5.3.3 Combined interventions

Integrating diet, exercise, and cognitive training—seem to offer the most comprehensive benefits. Research indicates that multimodal interventions can improve cognitive function and overall health outcomes in patients with T2DM (80). The LIFE study, which included physical activity interventions, reported beneficial effects on global cognitive function and memory slowing in elderly individuals with T2DM, highlighting the potential of a combined approach (84).

Current evidence positions multimodal lifestyle interventions as clinically actionable strategies for addressing diabetes-associated cognitive impairment. The triad of dietary optimization, structured exercise, and cognitive engagement demonstrates synergistic neuroprotection, potentially delaying dementia onset while improving metabolic health. Future research should prioritize protocol standardization.

6 Biomarkers of cognitive impairment in T2DM

Given the significantly increased risk of dementia and cognitive decline in patients with T2DM, research on predictive biomarkers and early detection technologies for cognitive impairment in this population

has gained increasing attention in recent years, which is of great significance for achieving early diagnosis and timely intervention. Recent research advances have revealed several categories of biomarkers with potential clinical applications, including but not limited to Neuron-Derived Exosomes (NDEs) and metabolic signatures.

NDEs are small extracellular vesicles that can cross the blood-brain barrier and are enriched with neuron-specific proteins, RNAs, and other biomolecules. These vesicles have emerged as promising tools for early diagnosis of neurodegenerative diseases (85). Chi et al. discovered that plasma NDEs from T2DM patients showed significantly reduced levels of mitochondrial complex I protein NDUFS3 and complex II protein SDHB. Lower SDHB levels were positively correlated with progression from MCI to AD (86). Specific miRNAs and proteins in NDEs, including but not limited to miR-185-5p, miR-132-3p, and miR-34a-5p (87–89), have been linked to AD and cognitive impairment, highlighting their biomarker potential.

Elevated myo-inositol (MI) concentrations coupled with reduced glutamate (Glu), Glx (glutamate + glutamine), and NAA/Cr (N-acetylaspartate/creatine) ratios within the hippocampus represent sensitive metabolic biomarkers for monitoring diabetic cognitive impairment progression (90). Additional metabolic biomarkers under consideration include C-reactive protein, tau protein, BDNF and AGEs (91).

The hippocampus, a brain region critically involved in learning and memory processes, may serve as an early "warning indicator" for diabetes-associated cognitive impairment through its volumetric changes (92). High-resolution MRI segmentation analyses have demonstrated significant volumetric reductions in memory-critical hippocampal subfields (CA1, dentate gyrus [DG], and subiculum) among middle-aged T2DM patients. These specific subregions are known to be fundamentally involved in memory encoding and consolidation processes. These structurally measured hippocampal subfield atrophies not only directly correlated with cognitive performance but may also reflect persistent neural damage caused by glucose metabolic dysregulation. Importantly, these findings provide neuroimaging evidence for early identification of high-risk populations (93).

In newly diagnosed T2DM patients, elevated venular tortuosity shows significant association with cognitive impairment. This correlation remained significant after adjustment for multiple demographic and health factors, suggesting retinal vascular tortuosity may serve as an early indicator of cognitive decline (94). Retinal vascular metrics (RVMs) can function as imaging biomarkers to predict cognitive impairment in T2DM, thereby enhancing risk stratification (95). Furthermore, patients with T2DM and mild cognitive impairment (MCI) exhibit significant thinning of the macular retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) (96). These structural changes can be effectively quantified through *in vivo* optical coherence tomography (OCT) imaging, highlighting the potential of retinal assessment for predicting diabetes-related cognitive dysfunction (97).

The complexity of T2DM-related cognitive dysfunction involves multiple pathways and contributing factors, necessitating a multi-faceted approach to biomarker discovery. Future research should prioritize validation of these biomarkers in larger longitudinal cohorts and explore their potential for guiding personalized therapeutic strategies.

7 Conclusion

In summary, a complex pathophysiological relationship exists between T2DM and cognitive impairment. Mechanisms including insulin resistance, chronic inflammation, vascular injury, and oxidative stress collectively drive disease progression. Effective glycemic control not only mitigates metabolic dysregulation but also exerts protective effects on cognitive function. Concurrently, factors such as age, educational attainment, and socioeconomic determinants play pivotal roles in disease development, thereby providing new perspectives for multidimensional intervention strategies. Furthermore, the discovery of novel biomarkers and early detection technologies offers promising avenues for early screening and disease monitoring.

These findings hold significant implications for both clinical practice and public health: On the one hand, they underscore the necessity for early cognitive assessment and integrated management in T2DM patients; On the other hand, they emphasize the importance of establishing social support systems to reduce cognitive risk in high-risk populations. However, current research still has limitations, such as small sample sizes in longitudinal cohort studies, incomplete understanding of mechanistic differences across diverse ethnic groups, and the need for further validation of newly identified biomarkers in clinical translation.

Future research could focus on leveraging multi-omics technologies to explore novel pathogenic mechanisms, conducting long-term, multicenter, cross-cultural cohort studies to clarify the universality of risk factors, and developing early warning models based on emerging biomarkers. There is also an urgent need to explore personalized comprehensive treatment strategies that integrate metabolic regulation and social interventions, thereby providing a more robust theoretical and practical foundation for improving cognitive health in patients with T2DM.

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