

**COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES MELLITUS:
PATHOPHYSIOLOGICAL MECHANISMS AND EMERGING
DIAGNOSTIC APPROACHES**

Telmanova Navbakhar,

Parpiyeva Yulduz Ravshanovna

Department of Neurology and Medical Psychology, Tashkent State

Medical University, Tashkent, Uzbekistan

E-mail: navbahortelmanova@gmail.com

Phone: +998905776626

Annotation: *Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with multiple systemic complications, including cognitive impairment. Increasing evidence suggests that patients with T2DM have a higher risk of memory dysfunction, reduced executive function, and dementia. Chronic hyperglycemia, insulin resistance, oxidative stress, neuroinflammation, and vascular dysfunction contribute significantly to neuronal injury and cognitive decline. Early diagnosis of cognitive impairment in diabetic patients remains challenging because neurological changes may develop gradually over many years. This review article summarizes current evidence regarding the pathophysiological mechanisms linking T2DM and cognitive dysfunction, discusses major risk factors and core blood/neuroimaging biomarkers, and highlights emerging diagnostic technologies and personalized preventive strategies. This review article provides an integrated roadmap for early clinical risk assessment and modern multimodal diagnostic models to mitigate the progression of diabetes-associated neurodegeneration.*

Keywords: Type 2 diabetes mellitus, Cognitive impairment, Neuroinflammation, Insulin resistance, Type 3 diabetes, Plasma biomarkers, Neuroimaging.

Introduction

Type 2 diabetes mellitus represents one of the most common chronic diseases worldwide and poses a major public health challenge. In addition to cardiovascular, renal, and peripheral neurological complications, increasing attention has been directed toward the effects of diabetes on the central nervous system. Cognitive impairment has become an important complication of T2DM, especially among elderly patients. Cognitive dysfunction in diabetic patients may involve memory loss, reduced attention, impaired executive function, slower information processing, and decreased learning ability. Several epidemiological studies demonstrate that patients with T2DM have an increased risk of developing mild cognitive impairment (MCI) and progressive dementia, including Alzheimer's disease (AD) and vascular dementia.

The mechanisms responsible for diabetes-associated cognitive decline are multifactorial and involve chronic hyperglycemia, systemic and central insulin resistance, oxidative stress, neuroinflammation, endothelial dysfunction, and macro/microvascular injury. Despite growing scientific interest, early diagnosis and prevention of cognitive decline in diabetic patients remain difficult since standard cognitive tests often fail to capture subtle subclinical neurodegenerative changes. The aim of this review is to summarize current knowledge regarding the relationship between type 2 diabetes mellitus and cognitive impairment, focusing on molecular pathophysiological mechanisms, validated fluid and imaging biomarkers, modern diagnostic tools, and future therapeutic perspectives.

Methods

This review article was prepared using scientific literature obtained from PubMed, Google Scholar, and PMC databases. Articles published between 2014 and 2026 related to type 2 diabetes mellitus, cognitive impairment, neuroinflammation, oxidative stress, and diabetes-associated dementia were analyzed.

The following keywords and controlled syntax terms were utilized during the literature search: 'type 2 diabetes mellitus', 'cognitive impairment', 'diabetes and dementia', 'neuroinflammation', 'oxidative stress', 'insulin resistance and brain function', and 'plasma biomarkers'.

A total of 165 articles were initially screened by title and abstract. Following strict evaluation based on inclusion criteria (English language, peer-reviewed original clinical research, randomized controlled trials, and high-impact systemic reviews) and exclusion criteria (lack of scientific relevance or focus solely on Type 1 diabetes), 50 articles were comprehensively synthesized into this review.

Results and Discussion

Hyperglycemia and Cognitive Dysfunction

Chronic hyperglycemia plays a foundational role in the development of cognitive impairment in T2DM patients. Persistent elevation of blood glucose levels contributes to structural and functional neuronal damage through multiple aberrant metabolic pathways. Hyperglycemia accelerates the formation of advanced glycation end products (AGEs), which progressively accumulate in neural tissues and cross-link with extracellular matrix proteins, directly impairing synaptic plasticity and long-term potentiation. Furthermore, long-term hyperglycemia inflicts severe damage upon cerebral microvessels, reducing nutrient and oxygen supply across the blood-brain barrier (BBB) and contributing to progressive ischemic cognitive decline. Several longitudinal

clinical studies demonstrate a proportional, direct association between elevated baseline HbA1c levels and reduced cognitive performance.

Insulin Resistance and Brain Function

Insulin is essential not only for peripheral glucose homeostasis but also for normal neuronal survival, synaptic vesicle regulation, and cognitive plasticity. Insulin receptors are densely expressed within the hippocampus, cerebral cortex, and olfactory bulb—brain regions critically responsible for memory consolidation and spatial learning. In T2DM, central insulin resistance disrupts regular downstream intracellular signaling cascades (such as the PI3K/Akt pathway), impairing neuronal glucose utilization and disrupting neurotransmitter homeostasis. This metabolic collapse blocks synaptic plasticity, promotes amyloid-beta accumulation, and accelerates abnormal tau hyperphosphorylation. Because of these overlapping molecular pathologies, many researchers now characterize Alzheimer's disease as 'Type 3 Diabetes' to emphasize the central role of brain insulin resistance.

Oxidative Stress and Neuroinflammation

Oxidative stress represents a critical intermediary mechanism linking metabolic dysfunction with structural brain decline. Excessive production of reactive oxygen species (ROS) driven by mitochondrial overload overpowers endogenous antioxidant systems, directly damaging neuronal cell membranes, critical enzymes, and cerebral endothelial cells. In parallel, neuroinflammation actively drives cognitive deterioration. Hyperglycemia and circulating AGEs trigger microglial activation, stimulating the continuous release of elevated pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and systemic C-reactive protein (CRP). Chronic exposure to this localized inflammatory environment accelerates neurodegeneration, destroys synaptic contacts, and profoundly disrupts executive cognitive function.

Vascular Dysfunction and Structural Brain Changes

Microvascular and macrovascular complications of diabetes profoundly alter cerebral macro-hemodynamics and local microcirculation. Endothelial disrepair, accelerated atherosclerosis, and compromised cerebral blood flow lead to localized micro-infarcts, lacunar strokes, and diffuse white matter damage (leukoaraiosis).

Neuroimaging data confirms that diabetic patients exhibit characteristic structural brain changes, including generalized cerebral atrophy, cortical thinning, and accelerated reduction in hippocampal volume. These structural lesions directly translate into marked clinically observable deficits in memory recall, mental processing speed, and executive control.

Table 1: Pathophysiological Mechanisms and Cognitive Consequences in T2DM

Pathophysiological Mechanism	Core Biomarkers / Indicators	Cerebral Pathological Changes	Clinical Cognitive Consequences
Hyperglycemia	AGEs, Elevated HbA1c	Synaptic damage, linking, blood-brain barrier breakdown.	Reduced mental processing speed, deficits in learning capacity.

Pathophysiological Mechanism	Core Biomarkers / Indicators	Cerebral Pathological Changes	Clinical Cognitive Consequence
Insulin Resistance	PI3K/Akt down-regulation	Impaired neuronal glucose uptake, tau hyperphosphorylation, amyloid plaque formation.	Severe short-term memory impairment, high risk of progression to Alzheimer's.
Oxidative Stress & Neuroinflammation	ROS, IL-6, TNF- α , CRP	Mitochondrial failure, chronic microglial activation, synaptic destruction.	Loss of attention concentration, working memory deficits.
Vascular Dysfunction	Endothelial dysfunction markers	White matter hyperintensities (WMH), cerebral micro-infarcts, hippocampal atrophy.	Executive dysfunction, impaired judgment, vascular dementia.

Biomarkers and Emerging Diagnostic Approaches

Early detection of metabolic cognitive decline requires moving beyond basic screening to comprehensive multimodal profiles:

- **Glycemic and Metabolic Profile (HbA1c, AGEs):** Long-term glycemic tracking and advanced glycation monitoring remain core indicators of baseline risk.
- **Circulating Cytokines (IL-6, TNF- α , CRP):** Tracking neuroinflammatory activity provides practical insights into the rate of ongoing tissue damage.
- **Plasma Neurodegenerative Markers (Amyloid-beta, p-tau fractions):** Traditionally limited to cerebrospinal fluid (CSF), modern ultra-sensitive blood-based assays (like Simoa) now enable the detection of plasma phosphorylated-tau (p-tau181, p-tau217) and Amyloid-beta (A β 42/A β 40 ratio) directly from blood, acting as an effective 'liquid biopsy' for subclinical neurodegeneration.
- **Advanced Neuroimaging (MRI and PET):** High-resolution structural Magnetic Resonance Imaging (MRI) is utilized to track early hippocampal volume loss and white matter hyperintensities (WMH). Meanwhile, Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) reveals regional cerebral hypometabolism long before structural atrophy occurs.
- **Artificial Intelligence (AI) Risk Prediction:** By training machine learning models on large datasets containing multi-omics, cognitive scores, and lifestyle data, clinicians can accurately calculate personalized predictive risk curves for cognitive decay.

Prevention and Therapeutic Perspectives

Achieving strict, early glycemic control is vital to protect central neural circuits from irreversible damage. Multi-domain lifestyle interventions—including customized resistance exercise, antioxidant-dense diets, cognitive training, and strict vascular risk reduction—show proven efficacy in stabilizing cognitive capacity. Importantly, specific classes of antidiabetic drugs have revealed direct neuroprotective properties. Metformin diminishes central

oxidative pathways and supports neurogenesis. Furthermore, GLP-1 receptor agonists (such as liraglutide and semaglutide) can cross the blood-brain barrier to directly lower neuroinflammation, enhance brain insulin signaling, and protect synaptic architecture. Future management must build upon biomarker-guided, personalized metabolic regimens.

Conclusion

Cognitive impairment is an increasingly recognized, highly debilitating complication of type 2 diabetes mellitus that significantly reduces functional independence and quality of life. Chronic hyperglycemia, central insulin resistance, mitochondrial oxidative stress, cytokine-mediated neuroinflammation, and progressive macro/microvascular dysfunction act synergistically to drive structural brain degradation. The ongoing integration of ultra-sensitive plasma neurodegenerative biomarkers (p-tau, Amyloid-beta ratios), advanced functional neuroimaging, and artificial intelligence risk modeling provides a robust framework for early, pre-symptomatic detection. Future clinical efforts must prioritize validated multi-modal diagnostic screening panels and early neuroprotective metabolic interventions to reduce the long-term global burden of diabetes-associated dementia.

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