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Diabetes-Induced Neurodegeneration: Linking Hyperglycemia to Cognitive Impairment and Brain Aging

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is increasingly recognized not only as a metabolic disorder but also as a significant risk factor for neurodegeneration and cognitive decline. Chronic hyperglycemia, insulin resistance, and systemic inflammation—hallmarks of T2DM—have been implicated in the pathogenesis of brain aging, mild cognitive impairment (MCI), and various forms of dementia, including Alzheimer's disease. This review provides a comprehensive synthesis of current evidence linking diabetes to neurodegeneration, elucidating the pathophysiological pathways through which hyperglycemia and impaired insulin signaling adversely affect brain structure and function. Mechanisms explored include oxidative stress, advanced glycation end-products (AGEs), mitochondrial dysfunction, blood-brain barrier disruption, and neuroinflammation. Emerging neuroimaging findings, biomarkers, and preclinical models are discussed to illustrate structural and functional brain alterations in diabetic populations. Moreover, the role of central insulin resistance, hippocampal atrophy, and impaired neurogenesis are emphasized as key contributors to diabetes-related cognitive impairment. Finally, the review examines therapeutic strategies, including glycemic control, anti-inflammatory agents, and neuroprotective interventions, aiming to mitigate neurodegenerative outcomes in diabetic patients. Understanding the intersection of metabolic and cognitive dysfunction holds promise for early detection, prevention, and integrative management of diabetes-induced brain aging.

Keywords: Hyperglycemia, Central insulin resistance, Neuroinflammation, Cognitive decline, Oxidative stress

INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a chronic metabolic condition with increasing global prevalence [1]. It is currently estimated that over 500 million adults are living with diabetes, and this number is projected to rise significantly in the coming decades [2]. Traditionally viewed as a disease primarily affecting blood sugar control, diabetes has now been shown to have extensive systemic implications. Among these, the impact of diabetes on the central nervous system (CNS) has gained substantial interest. Accumulating evidence suggests that T2DM not only increases the risk of macrovascular and microvascular complications but also plays a significant role in accelerating neurodegeneration and cognitive decline [3]. The association between diabetes and cognitive dysfunction is supported by both epidemiological data and mechanistic studies. Patients with T2DM have a higher risk of developing mild cognitive impairment (MCI), Alzheimer's disease (AD), and other forms of dementia [4]. The mechanisms underlying this association are multifactorial and include chronic hyperglycemia, insulin resistance, oxidative stress, inflammation, and vascular injury [5]. Importantly, these pathophysiological processes contribute to brain structural changes, including hippocampal atrophy and cortical thinning, which are hallmarks of cognitive aging and dementia [6]. This review aims to provide a detailed analysis of how diabetes leads to neurodegeneration, with particular attention to the molecular and cellular mechanisms involved. The discussion will also explore how neuroimaging and biomarker studies have enhanced our understanding of diabetes-related brain changes. Finally, we will consider current and emerging therapeutic strategies aimed at preventing or mitigating neurodegenerative changes in individuals with diabetes.

Pathophysiology of Hyperglycemia-Induced Neurodegeneration

Chronic hyperglycemia, the defining feature of diabetes, initiates a cascade of detrimental effects on neuronal integrity and function [7]. The persistent elevation of blood glucose levels results in the excessive production of reactive oxygen species (ROS), which causes oxidative stress [8]. Neurons are particularly susceptible to oxidative damage due to their high metabolic activity and limited antioxidant capacity [9]. ROS interfere with mitochondrial function, disrupt ATP production, and damage critical cellular components including proteins, lipids, and nucleic acids [10]. In addition to oxidative stress, hyperglycemia promotes the non-enzymatic glycation of proteins and lipids, leading to the formation of advanced glycation end-products (AGEs) [11]. AGEs accumulate in the brain and bind to their specific receptors (RAGE), triggering intracellular signaling pathways that promote inflammation and cell death [12]. The AGE-RAGE interaction also exacerbates oxidative stress, forming a vicious cycle that further injures neurons and glial cells [13].

Hyperglycemia also affects the structure and function of the blood-brain barrier (BBB). Under normal physiological conditions, the BBB serves as a selective barrier that protects the brain from circulating toxins and pathogens [14]. In diabetes, hyperglycemia-induced endothelial dysfunction leads to increased BBB permeability. This allows the entry of inflammatory mediators, immune cells, and potentially harmful substances into the brain parenchyma, thereby amplifying neuroinflammation [15]. Another key consequence of chronic hyperglycemia is impaired insulin signaling in the brain [16]. Insulin has several roles in the CNS, including regulation of synaptic plasticity, neurotransmitter release, and neuronal survival [17]. Disruption of insulin signaling due to sustained hyperglycemia leads to synaptic deficits, reduced neurogenesis, and increased neuronal apoptosis [18]. This impairment is particularly evident in the hippocampus, a brain region essential for learning and memory.

Central Insulin Resistance and Brain Aging

Central insulin resistance, a condition in which brain cells exhibit diminished responsiveness to insulin, is increasingly recognized as a pivotal factor in diabetes-related neurodegeneration [19]. Unlike peripheral insulin resistance that affects glucose uptake in muscles and adipose tissue, central insulin resistance impacts neuronal energy metabolism and synaptic function. Insulin is essential for promoting neuronal glucose uptake, facilitating synaptic plasticity, and regulating key neurotransmitters such as acetylcholine and glutamate [20]. In the diabetic brain, insulin signaling is impaired due to receptor downregulation, post-receptor signaling defects, or increased insulin-degrading enzyme activity [21]. This results in energy deficits, as glucose utilization becomes inefficient. Neurons deprived of energy cannot maintain normal electrical and biochemical activity, leading to dysfunction and eventual death. The hippocampus, which contains a high density of insulin receptors, is particularly vulnerable to insulin resistance, explaining the early memory deficits observed in diabetic patients [22]. Neuroimaging studies support these findings. Patients with T2DM exhibit significant structural brain changes, including reduced hippocampal volume, cortical thinning, and ventricular enlargement [23]. Functional MRI studies show altered connectivity in neural circuits responsible for memory and executive function. Positron emission tomography (PET) studies also reveal reduced glucose metabolism in the brains of insulin-resistant individuals, a feature that overlaps with patterns seen in Alzheimer's disease [24]. The mechanisms linking central insulin resistance to neurodegeneration also involve disruptions in the insulin-like growth factor-1 (IGF-1) signaling pathway [25]. IGF-1 supports neurodevelopment, synaptic repair, and neuroprotection. Impairments in this pathway reduce neurogenesis and increase vulnerability to neurotoxins [26]. Additionally, insulin resistance is associated with increased amyloid precursor protein processing and tau phosphorylation, both of which are pathological hallmarks of Alzheimer's disease [27].

Neuroinflammation and Oxidative Stress

Neuroinflammation and oxidative stress are two interrelated mechanisms that play central roles in the neurodegenerative consequences of diabetes. Inflammatory responses in the brain are primarily mediated by microglia, the resident immune cells of the CNS [28]. In response to hyperglycemia and metabolic stress, microglia become activated and shift to a pro-inflammatory phenotype [29]. This activation results in the production of cytokines such as IL-1β, TNF-α, and IL-6, which contribute to neuronal injury and synaptic dysfunction. Simultaneously, oxidative stress induced by hyperglycemia enhances microglial activation and perpetuates inflammatory signaling [30]. The imbalance between ROS production and antioxidant defense mechanisms leads to cellular damage in neurons and glial cells [31]. This includes lipid peroxidation, protein oxidation, and DNA fragmentation, all of which impair cellular function and viability.

Moreover, astrocytes—another major glial cell type—undergo reactive changes in response to oxidative and inflammatory stress [32]. Reactive astrocytes contribute to the formation of glial scars, disrupt neurotransmitter homeostasis, and further impair neuronal communication [33]. These changes affect not only individual neurons but also the integrity of entire neural networks. Chronic neuroinflammation and oxidative stress also contribute to the breakdown of the BBB [34]. As endothelial cells are damaged, the BBB becomes more permeable, allowing further infiltration of peripheral immune cells and pro-inflammatory mediators [35]. This breach in the CNS's protective barrier compounds the inflammatory milieu and accelerates neurodegeneration.

Collectively, the interplay between oxidative stress and neuroinflammation forms a self-amplifying loop that underlies much of the cognitive dysfunction observed in diabetes. Targeting these pathways with anti-inflammatory and antioxidant therapies offers a promising approach for neuroprotection in diabetic individuals.

Role of Advanced Glycation End-products (AGEs)

AGEs are formed through non-enzymatic glycation of proteins and lipids in hyperglycemic conditions [36]. These products accumulate in various tissues, including the brain, and interact with RAGE to trigger inflammatory and apoptotic pathways. In the CNS, AGEs impair synaptic function, reduce neuronal viability, and contribute to amyloid-beta aggregation—a hallmark of Alzheimer's pathology [37]. In diabetic patients, elevated serum and cerebrospinal fluid (CSF) levels of AGEs correlate with poorer cognitive performance and structural brain changes [38]. AGEs also enhance tau phosphorylation, further linking diabetes to Alzheimer's disease pathogenesis [39]. Thus, targeting AGE-RAGE interactions may provide a therapeutic avenue for mitigating diabetes-related neurodegeneration.

Structural and Functional Brain Changes in Diabetes

Neuroimaging studies using MRI and PET have revealed significant structural and functional brain alterations in individuals with T2DM. Common findings include: Hippocampal atrophy, Reduced total brain volume, White matter hyperintensities, Ventricular enlargement, Decreased cerebral glucose metabolism [40]. These changes are associated with deficits in memory, executive function, processing speed, and attention. Functional connectivity studies have also shown disrupted neural network activity, particularly in the default mode network (DMN) and frontoparietal networks, which are critical for cognitive integration and task execution [41].

Cognitive Impairment and Clinical Manifestations

Cognitive decline in diabetes ranges from mild cognitive impairment (MCI) to dementia [42]. MCI in diabetic patients often presents with executive dysfunction, memory disturbances, and impaired attention [43]. Longitudinal studies indicate that individuals with diabetes and MCI have a higher rate of progression to dementia [44]. Diabetes is also associated with an increased risk of vascular dementia due to its impact on cerebrovascular health [45]. Microangiopathy, endothelial dysfunction, and cerebral small vessel disease are common in diabetic populations, further compounding the risk of cognitive impairment [46].

Therapeutic Strategies

Given the multifactorial nature of diabetes-induced neurodegeneration, therapeutic interventions must be multi-pronged. Glycemic control remains a cornerstone of management. Studies have shown that intensive glucose control reduces the risk of cognitive decline, although the benefits must be weighed against the risk of hypoglycemia, which itself can impair cognition [47]. Anti-inflammatory and antioxidant therapies, including polyphenols (e.g., resveratrol, curcumin), omega-3 fatty acids, and certain antidiabetic agents (e.g., metformin, GLP-1 receptor agonists), have shown neuroprotective effects in preclinical and early clinical studies [48]. Intranasal insulin delivery is being explored as a novel approach to restore central insulin signaling without peripheral side effects. Neurotrophic agents, cognitive training, physical exercise, and dietary interventions are additional strategies under investigation.

CONCLUSION

T2DM significantly contributes to neurodegeneration and cognitive decline through mechanisms involving hyperglycemia, insulin resistance, oxidative stress, and neuroinflammation. The brain is a metabolically sensitive organ, and disruptions in glucose homeostasis and insulin signaling have profound implications for cognitive function and brain aging. Recognizing the neurocognitive consequences of diabetes is essential for early diagnosis, preventive care, and the development of targeted therapies. An integrative, multidisciplinary approach combining metabolic control, lifestyle modification, and neuroprotective strategies holds promise for reducing the burden of diabetes-induced neurodegeneration.

REFERENCES

1. Umegaki H. Type 2 diabetes as a risk factor for cognitive impairment: current insights. Clinical Interventions in Aging. 2014;1011. doi:10.2147/cia.s48926
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice. 2019;157:107843. doi:10.1016/j.diabres.2019.107843
3. Meng X, Du H, Li D, Guo Y, Luo P, Pan L, et al. Risk factors, pathological changes, and potential treatment of diabetes-associated cognitive dysfunction. Journal of Diabetes. 2025;17(4). doi:10.1111/1753-0407.70089
4. PMC Copyright Notice – PMC. Available from: https://pmc.ncbi.nlm.nih.gov/about/copyright/
5. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. International Journal of Molecular Sciences. 2020;21(17):6275. doi:10.3390/ijms21176275

6. Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA. A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nature Reviews Neuroscience. 2011;12(10):585–601. doi:10.1038/nrn3085
7. Aderinto N, Olatunji G, Abdulbasit M, Ashinze P, Faturoti O, Ajagbe A, et al. The impact of diabetes in cognitive impairment: a review of current evidence and prospects for future investigations. Medicine. 2023;102(43):e35557. doi:10.1097/MD.0000000000035557
8. Ikpozu EN, Offor CE, Igwenyi IO, Ibiam UA, Obaroh IO. RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 2025;22(2). doi:10.1177/14791641251334726
9. Garbarino VR, Orr ME, Rodriguez KA, Buffenstein R. Mechanisms of oxidative stress resistance in the brain: lessons learned from hypoxia tolerant extremophilic vertebrates. Archives of Biochemistry and Biophysics. 2015;576:8–16. doi:10.1016/j.abb.2015.01.029
10. Zhou H, Wu C, Jin Y, Wu O, Chen L, Guo Z, et al. Role of oxidative stress in mitochondrial dysfunction and their implications in intervertebral disc degeneration: mechanisms and therapeutic strategies. Journal of Orthopaedic Translation. 2024;49:181–206. doi:10.1016/j.jot.2024.08.016
11. Alum EU. Optimizing patient education for sustainable self-management in type 2 diabetes. *Discov Public Health* **22**, 44 (2025). https://doi.org/10.1186/s12982-025-00445-5
12. Zhou M, Zhang Y, Shi L, Li L, Zhang D, Gong Z, et al. Activation and modulation of the AGEs-RAGE axis: implications for inflammatory pathologies and therapeutic interventions – a review. Pharmacological Research. 2024;206:107282. doi:10.1016/j.phrs.2024.107282
13. Wang B, Jiang T, Qi Y, Luo S, Xia Y, Lang B, et al. AGE-RAGE axis and cardiovascular diseases: pathophysiologic mechanisms and prospects for clinical applications. Cardiovascular Drugs and Therapy. 2024. doi:10.1007/s10557-024-07639-0
14. Dotiwala AK, McCausland C, Samra NS. Anatomy, head and neck: blood brain barrier. StatPearls – NCBI Bookshelf. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519556/
15. Bogush M, Heldt NA, Persidsky Y. Blood–brain barrier injury in diabetes: unrecognized effects on brain and cognition. Journal of Neuroimmune Pharmacology. 2017;12(4):593–601. doi:10.1007/s11481-017-9752-7
16. Gupta M, Pandey S, Rumman M, Singh B, Mahdi AA. Molecular mechanisms underlying hyperglycemia associated cognitive decline. IBRO Neuroscience Reports. 2022;14:57–63. doi:10.1016/j.ibneur.2022.12.006
17. Duarte AI, Moreira PI, Oliveira CR. Insulin in central nervous system: more than just a peripheral hormone. Journal of Aging Research. 2012;2012:1–21. doi:10.1155/2012/384017
18. Zhang S, Zhang Y, Wen Z, Yang Y, Bu T, Bu X, et al. Cognitive dysfunction in diabetes: abnormal glucose metabolic regulation in the brain. Frontiers in Endocrinology. 2023;14. doi:10.3389/fendo.2023.1192602
19. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nature Reviews Neurology. 2018;14(3):168–81. doi:10.1038/nrneurol.2017.185
20. Ferrario CR, Reagan LP. Insulin-mediated synaptic plasticity in the CNS: anatomical, functional and temporal contexts. Neuropharmacology. 2017;136:182–91. doi:10.1016/j.neuropharm.2017.12.001
21. De Meyts P. The insulin receptor and its signal transduction network. Endotext – NCBI Bookshelf. 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK378978/
22. Liu Q, Wang Z, Cao J, Dong Y, Chen Y. The role of insulin signaling in hippocampal-related diseases: a focus on Alzheimer's disease. International Journal of Molecular Sciences. 2022;23(22):14417. doi:10.3390/ijms232214417
23. Mahmood S, Dkhar W, Kadavigere R, Sukumar S, Nayak K, Pradhan A, et al. An analysis of brain structural changes in type 2 diabetes using advanced MRI techniques. Magnetic Resonance Imaging. 2025;121:110419. doi:10.1016/j.mri.2025.110419
24. Soltani S, Dolatshahi M, Soltani S, Khazaei K, Rahmani M, Raji CA. Relationships between brain glucose metabolism patterns and impaired glycemic status: a systematic review of FDG-PET studies with a focus on Alzheimer's disease. Human Brain Mapping. 2025;46(4). doi:10.1002/hbm.70180
25. Matioli MNPS, Nitrini R. Mechanisms linking brain insulin resistance to Alzheimer's disease. Dementia & Neuropsychologia. 2015;9(2):96–102. doi:10.1590/1980-57642015dn92000003
26. Ge L, Liu S, Rubin L, Lazarovici P, Zheng W. Research progress on neuroprotection of insulin-like growth factor-1 towards glutamate-induced neurotoxicity. Cells. 2022;11(4):666. doi:10.3390/cells11040666
27. Mullins RJ, Diehl TC, Chia CW, Kapogiannis D. Insulin resistance as a link between amyloid-beta and tau pathologies in Alzheimer's disease. Frontiers in Aging Neuroscience. 2017;9. doi:10.3389/fnagi.2017.00118

28. Biswas K. Microglia mediated neuroinflammation in neurodegenerative diseases: a review on the cell signaling pathways involved in microglial activation. Journal of Neuroimmunology. 2023;383:578180. doi:10.1016/j.jneuroim.2023.578180
29. Tian Y, Jing G, Ma M, Yin R, Zhang M. Microglial activation and polarization in type 2 diabetes-related cognitive impairment: a focused review of pathogenesis. Neuroscience & Biobehavioral Reviews. 2024;165:105848. doi:10.1016/j.neubiorev.2024.105848
30. González P, Lozano P, Ros G, Solano F. Hyperglycemia and oxidative stress: an integral, updated and critical overview of their metabolic interconnections. International Journal of Molecular Sciences. 2023;24(11):9352. doi:10.3390/ijms24119352
31. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, et al. Oxidative stress and inflammation in the pathogenesis of neurological disorders: mechanisms and implications. Acta Pharmaceutica Sinica B. 2024;15(1):15–34. doi:10.1016/j.apsb.2024.10.004
32. Lee KH, Cha M, Lee BH. Crosstalk between neuron and glial cells in oxidative injury and neuroprotection. International Journal of Molecular Sciences. 2021;22(24):13315. doi:10.3390/ijms222413315
33. Cieri MB, Ramos AJ. Astrocytes, reactive astrogliosis, and glial scar formation in traumatic brain injury. Neural Regeneration Research. 2024;20(4):973–89. doi:10.4103/nrr.nrr-d-23-02091
34. Kim S, Jung UJ, Kim SR. Role of oxidative stress in blood–brain barrier disruption and neurodegenerative diseases. Antioxidants. 2024;13(12):1462. doi:10.3390/antiox13121462
35. Galea I. The blood–brain barrier in systemic infection and inflammation. Cellular and Molecular Immunology. 2021;18(11):2489–501. doi:10.1038/s41423-021-00757-x
36. Khalid M, Petroianu G, Adem A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. Biomolecules. 2022;12(4):542. doi:10.3390/biom12040542
37. Zhang H, Jiang X, Ma L, Wei W, Li Z, Chang S, et al. Role of Aβ in Alzheimer's-related synaptic dysfunction. Frontiers in Cell and Developmental Biology. 2022;10. doi:10.3389/fcell.2022.964075
38. Moheet A, Mangia S, Seaquist ER. Impact of diabetes on cognitive function and brain structure. Annals of the New York Academy of Sciences. 2015;1353(1):60–71. doi:10.1111/nyas.12807
39. Hobday AL, Parmar MS. The link between diabetes mellitus and TAU hyperphosphorylation: implications for risk of Alzheimer's disease. Cureus. 2021. doi:10.7759/cureus.18362
40. Lee JH, Choi Y, Jun C, Hong YS, Cho HB, Kim JE, et al. Neurocognitive changes and their neural correlates in patients with type 2 diabetes mellitus. Endocrinology and Metabolism. 2014;29(2):112. doi:10.3803/enm.2014.29.2.112
41. Alahmadi A, Alali AG, Alzhrani BM, Alzhrani RS, Alsharif W, Aldahery S, et al. Unearthing the hidden links: investigating the functional connectivity between amygdala subregions and brain networks in bipolar disorder through resting-state fMRI. Heliyon. 2024;10(19):e38115. doi:10.1016/j.heliyon.2024.e38115
42. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nature Reviews Endocrinology. 2018;14(10):591–604. doi:10.1038/s41574-018-0048-7
43. Bashir J, Yarube IU. Occurrence of mild cognitive impairment with hyperinsulinaemia in Africans with advanced type 2 diabetes mellitus. IBRO Neuroscience Reports. 2022;12:182–7. doi:10.1016/j.ibneur.2022.02.003
44. Pal K, Mukadam N, Petersen I, Cooper C. Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. Social Psychiatry and Psychiatric Epidemiology. 2018;53(11):1149–60. doi:10.1007/s00127-018-1581-3
45. Cholerton B, Baker LD, Montine TJ, Craft S. Type 2 diabetes, cognition, and dementia in older adults: toward a precision health approach. Diabetes Spectrum. 2016;29(4):210–9. doi:10.2337/ds16-0041
46. Van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA. Cerebral microvascular complications of type 2 diabetes: stroke, cognitive dysfunction, and depression. The Lancet Diabetes & Endocrinology. 2020;8(4):325–36. doi:10.1016/S2213-8587(19)30405-X
47. Herzog RI, Sherwin RS. Can tight glycemic control in diabetes benefit cognition? Nature Reviews Neurology. 2012;8(3):124–6. doi:10.1038/nrneurol.2012.10
48. Blahova J, Martiniakova M, Babikova M, Kovacova V, Mondockova V, Omelka R. Pharmaceutical drugs and natural therapeutic products for the treatment of type 2 diabetes mellitus. Pharmaceuticals. 2021;14(8):806. doi:10.3390/ph14080806

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