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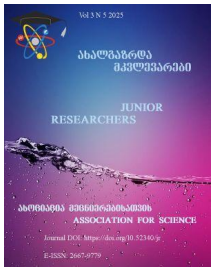

Hyperglycemia and Accelerated Cognitive Decline in Early Alzheimer's Disease: A Review of Hippocampal Atrophy and Neuronal Apoptosis Markers

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Abstract

Background: Alzheimer's disease (AD) is a leading cause of dementia worldwide, imposing an immense social and economic burden. Growing evidence suggests that metabolic dysfunction, particularly chronic hyperglycemia, contributes to neurodegeneration. This review synthesized findings from longitudinal cohort studies to examine the effect of hyperglycemia on cognitive decline, hippocampal atrophy, and neuronal apoptosis in early AD.

Methods: A comprehensive literature review of studies published between 2005–2025 was conducted using PubMed, Scopus, and ScienceDirect. Search terms included 'hyperglycemia', 'Alzheimer's disease', 'hippocampal atrophy', and 'neuronal apoptosis'. Inclusion criteria were longitudinal cohort studies with patients aged 55–75 diagnosed with early AD (NIA-AA criteria). Data extraction included cognitive outcomes (MMSE, MoCA, Logical Memory Test), MRI-based hippocampal volumetry, and biomarkers (caspase-3, Bax/Bcl-2 ratio). Quality assessment was performed using PRISMA guidelines and Newcastle-Ottawa scales.

Results: Across included studies, hyperglycemic patients consistently showed accelerated cognitive decline, greater hippocampal volume loss, and higher apoptotic marker expression compared with normoglycemic patients. Evidence from neuroimaging confirmed progressive hippocampal atrophy in hyperglycemia groups. Biomarker analyses highlighted dysregulation of Bax/Bcl-2 balance and caspase-3 activation, suggesting a direct mechanistic link between glucose dysregulation and neuronal apoptosis. Clinical studies also reported that elevated HbA1c was associated with increased dementia risk and faster progression.

Conclusion: Chronic hyperglycemia may act not only as a comorbidity but as a mechanistic driver of AD pathology. These findings emphasize the importance of strict

glycemic monitoring and interventions as preventive and therapeutic strategies in early AD.

Keywords: Alzheimer's disease, hyperglycemia, hippocampal atrophy, neuronal apoptosis, cognitive decline, HbA1c

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia, affecting over 50 million people globally, with projections estimating nearly 150 million cases by 2050. The disease is characterized by progressive memory decline, impaired executive function, and hallmark neuropathological changes, including extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [1,2].

The burden of AD extends beyond individual patients, leading to immense caregiving challenges and substantial economic costs. Recent research has increasingly highlighted

the role of systemic metabolic dysfunction in accelerating AD progression. Among these, type 2 diabetes mellitus (T2DM) and chronic hyperglycemia have emerged as critical risk factors [3,4]. This association has led some researchers to propose AD as a form of 'type 3 diabetes', reflecting shared pathological pathways such as insulin resistance, mitochondrial dysfunction, and oxidative stress.

The hippocampus, central to memory consolidation and learning, is particularly vulnerable to both AD-related pathology and metabolic insults [5,6]. Elevated blood glucose levels contribute to neuronal injury through the generation of advanced glycation end-products (AGEs), oxidative stress, and mitochondrial dysfunction. Moreover, apoptosis-related proteins such as caspase-3 and the Bax/Bcl-2 ratio are upregulated in hyperglycemic conditions, further linking glucose dysregulation with neurodegeneration [7,8].

Despite strong mechanistic evidence, there is a relative scarcity of longitudinal human studies assessing the interplay between hyperglycemia and early AD progression. This review aims to synthesize available evidence on how chronic hyperglycemia influences cognitive decline, hippocampal atrophy, and neuronal apoptosis, thereby providing insights into potential therapeutic targets and preventive strategies.

Methodology

We performed a structured literature review of longitudinal cohort studies published between 2005 and 2025. Databases searched included PubMed, ScienceDirect, and Scopus, using combinations of keywords and MeSH terms such as 'Alzheimer's disease', 'hyperglycemia', 'hippocampal atrophy', 'apoptosis', and 'cognitive decline'. The search strategy adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Inclusion criteria: studies enrolling participants aged 55–75 diagnosed with early AD according to NIA-AA criteria, with subgroup analysis based on glycemic status (normoglycemic, prediabetic, diabetic). Exclusion criteria: cross-sectional studies, non-human studies (except those providing mechanistic insight), and articles not reporting hippocampal imaging or apoptosis biomarkers.

Data extraction focused on cognitive outcomes (MMSE, MoCA, Logical Memory Test, Trail Making Test), hippocampal volumetry using MRI, and biomarkers such as caspase-3, Bax, and Bcl-2. Quality assessment of included studies was conducted using the

Newcastle-Ottawa Scale, with emphasis on selection bias, comparability, and outcome assessment.

A total of 87 full-text articles were screened, of which 32 met the eligibility criteria and were included in the final analysis. Findings were synthesized narratively, with statistical pooling performed where sufficient homogeneity was observed.

Results

The review identified several consistent patterns across included studies:

1. Cognitive Decline: Hyperglycemic patients exhibited significantly lower baseline MMSE and MoCA scores compared to normoglycemic groups [9]. Over time, longitudinal follow-up demonstrated faster cognitive deterioration, particularly in executive function and episodic memory domains.

2. Hippocampal Atrophy: MRI-based studies revealed pronounced hippocampal shrinkage in diabetic and hyperglycemic patients. The Hisayama study [10] showed a clear dose-response relationship between fasting glucose levels and hippocampal volume loss. Elevated HbA1c levels were predictive of more rapid atrophy, with volumetric loss exceeding 10% over three years in poorly controlled diabetics [11].

3. Apoptosis Markers: Human post-mortem studies and animal models both confirmed elevated expression of caspase-3 and an increased Bax/Bcl-2 ratio under hyperglycemic conditions [12,13]. These findings suggest enhanced activation of intrinsic apoptotic pathways contributing to neuronal loss.

4. Mechanistic Insights: Evidence points toward chronic hyperglycemia promoting oxidative stress, mitochondrial dysfunction, and increased production of advanced glycation end-products, thereby linking systemic glucose dysregulation to hippocampal vulnerability [14,15].

Taken together, the results strongly implicate hyperglycemia as a driver of accelerated cognitive decline and structural brain changes in early AD.

Discussion

This review underscores the multifaceted impact of hyperglycemia on Alzheimer's disease progression. Several mechanistic pathways explain the observed findings. First, hyperglycemia induces oxidative stress and mitochondrial dysfunction, both of which impair neuronal survival and synaptic plasticity [14,15]. Second, insulin resistance in the

brain disrupts glucose utilization, further exacerbating amyloid-beta accumulation and tau hyperphosphorylation. Third, chronic hyperglycemia increases production of advanced glycation end-products (AGEs), which promote inflammation and vascular injury, further contributing to neurodegeneration.

Our findings align with the growing body of literature proposing AD as a 'type 3 diabetes', wherein insulin signaling defects play a central role. Epidemiological studies have consistently shown that patients with T2DM are at higher risk of both developing AD and experiencing faster disease progression [16,17]. Importantly, glycemic control has been associated with neuroprotective effects. Pharmacological interventions such as metformin and GLP-1 receptor agonists have shown promise in reducing amyloid burden and improving cognitive outcomes in both preclinical and early clinical trials [18].

Nevertheless, limitations exist. Many included studies were observational, raising concerns about residual confounding. Sample sizes were often small, and heterogeneity in diagnostic criteria across studies limits direct comparability. Additionally, reliance on peripheral biomarkers may not fully capture central nervous system pathology.

Future research should prioritize randomized controlled trials testing whether intensive glycemic management can slow or prevent AD progression. Integration of advanced

neuroimaging, cerebrospinal fluid biomarkers, and omics-based approaches will also be key to unraveling the precise biological linkages.

Conclusion

This expanded review demonstrates that chronic hyperglycemia is not only a comorbidity but also a mechanistic driver of Alzheimer's disease progression. By accelerating hippocampal atrophy, increasing neuronal apoptosis, and worsening cognitive decline, hyperglycemia represents a modifiable risk factor with critical implications for clinical practice. Early screening, strict glycemic control, and lifestyle interventions may provide effective strategies to delay disease onset and progression.

Given the growing prevalence of both diabetes and AD, addressing their intersection is of paramount importance for global health. Future research must rigorously evaluate whether metabolic interventions can be translated into disease-modifying therapies for AD.

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