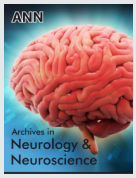

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Review Article

Chronic Hyperglycemia-Induced Oxidative Stress and Neurodegeneration in AD: Molecular Pathways and Mechanistic Interactions

Isha Jayakumar and Osayomore Marie LaCour*

University of Georgia College of Veterinary Medicine, Department of Physiology and Pharmacology, USA.

***Corresponding author:** Osayomore Marie LaCour, University of Georgia College of Veterinary Medicine, Department of Physiology and Pharmacology, USA.

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Abstract

The role of chronic hyperglycemia in the development of diabetes mellitus is critical, as it influences brain function by altering brain metabolism and signaling pathways. These changes can lead to synaptic dysfunction, resulting in communication problems between brain cells and cognitive impairment, including difficulties with memory, learning, and cognitive processing. Certain molecular events deluge metabolic pathways and mechanisms, such as activation of the polyol pathway, pro-oxidative stress processes, accumulation of advanced glycation end-products (AGEs), and the APOE4 gene. As a result, the interactive effects of these factors converge to form a feedback loop of dysfunction, cascading into metabolic, vascular, and neurodegenerative processes. Therefore, managing blood sugar through lifestyle changes and medication is also vital, along with targeting harmful processes such as AGE formation/inflammation.

Abbreviations: Aβ: Amyloid beta; AD: Alzheimer's Disease; AGE: Advanced Glycation End-Product; AGEs: Advanced Glycation End-Products ALS: Amyotrophic lateral sclerosis; ApoE: Apolipoprotein E; ApoE4: Apolipoprotein E epsilon 4 allele APP: Amyloid precursor protein; CDR: Clinical Dementia Rating CNS: Central nervous system CVD: Cardiovascular disease FTD: Frontotemporal dementia; GDM: Gestational diabetes mellitus GSH: Reduced glutathione; HD: Huntington's disease; HMGB1: High-mobility group box 1 IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; MAPK: Mitogen-activated protein kinase MetS: Metabolic syndrome; NAD+: Nicotinamide adenine dinucleotide (oxidized form); NADH: Nicotinamide adenine dinucleotide (reduced form); NF: KB: Nuclear factor kappa-light-chain-enhancer of activated B cells PD: Parkinson's disease; RAGE: Receptor for advanced glycation end-products ROS: Reactive oxygen species; T1DM: Type 1 diabetes mellitus T2DM: Type 2 diabetes mellitus TLR4: Toll-like receptor

Introduction

Chronic high blood sugar, or hyperglycemia, is a prominent feature of diabetes mellitus, which causes a series of changes in the body that affect more than just how sugar is processed. Consequently, these changes can cause damage to the neural network and increase the risk of brain diseases such as Alzheimer's disease (AD) (Verdile et al., 2015; Ito et al., 2019; Wu et al., 2024) [78,30,80].

When blood sugar levels remain high, several metabolic pathways become activated, including the biochemical polyol pathway. The polyol pathway facilitates the conversion of glucose to sorbitol and fructose by the enzyme aldose reductase, leading to the accumulation of these substances within cells. In turn, this shift in metabolism affects the balance of fluids within cells and utilizes Nicotinamide Adenine Dinucleotide Phosphate (NADPH), a reducing agent that protects the cell from oxidative damage and restores reduced glutathione, a powerful antioxidant within the cell (Wu et al., 2014) [80]. With less NADPH available, the cell's ability to fight off damage from reactive oxygen species (ROS) is reduced.

Moreover, the excessive production of ROS plays a crucial role in how elevated blood sugar contributes to neural dysfunction. High glucose levels cause mitochondria to function less efficiently and increase the activity of NADPH oxidase (NOX), which is essential for fighting infections yet can also contribute to oxidative stress when deregulated. Both components generate more ROS (Ito et al., 2019; Argaev-Frenkel & Rosenzweig, 2023) [30,3]. These harmful molecules damage fats, proteins, and DNA, which weakens the cells and disrupts their functions. In the brain, this oxidative stress amplifies neuroinflammation, contributing to neuronal injury and diabetic complications, including tissue damage, retinopathy, nephropathy, and peripheral neuropathy (Kowluru & Chan, 2007; Ting et al., 2018; Argaev-Frenkel & Rosenzweig, 2023) [7,73,3].

Furthermore, another process associated with brain dysfunction is persistent hyperglycemia in diabetes, which promotes the non-enzymatic glycation of proteins and lipids, leading to the formation of AGEs. When blood sugar levels remain high, sugars bind to proteins and fats in a reaction that does not require the presence of enzymes. The change in the mechanistic process results in the accumulation of AGEs, which can bind to other proteins in cells, altering their shape and function (Ito et al., 2019) [30]. This reaction escapes normal cellular regulation, leading to the progressive accumulation of AGEs and intermolecular cross-linking, which can disrupt regular protein conformation and function. Furthermore, AGEs bind to RAGE (Receptor for Advanced Glycation End-Products), triggering a chain of signals that lead to increased oxidative stress, inflammation, and cell death (Ito et al., 2019) [30]. Specifically, in AD, AGEs have been observed to increase the clumping of amyloid-beta (Aβ) and contribute to hyperphosphorylation, which occurs when tau protein becomes overloaded with phosphate groups, causing it to malfunction and clump together (Moreira et al., 2006; Ficiarà et al., 2025) [52,23]. Taken together, these processes – oxidative stress, inflammation, and glycation-driven protein conformational changes – form a self-reinforcing feed-forward loop that accelerates neurodegeneration in people with diabetes (Kowluru & Chan, 2007; Wu et al., 2014; Argaev-Frenkel & Rosenzweig, 2023) [38,80,3]. Genetic susceptibility, such as carriage of the ApoE4 gene, can further heighten the vulnerability to diabetes-associated brain injury (Ficiarà et al., 2025) [23].

Because of these interlinked effects, oxidative stress plays a significant role in both diabetes and AD, treatments that reduce this type of damage are ideal (Moreira et al., 2006) [52]. However, human studies show that antioxidant treatments alone provide limited benefits, suggesting that simultaneously targeting multiple pathways will likely yield more significant results (Argaev-Frenkel & Rosenzweig, 2023) [3]. Therefore, it is essential to keep blood sugar under control, as this remains crucial for preventing or delaying brain-related complications. There is a need for research and discovery of new therapies to address the underlying biological causes (Verdile et al., 2015) [78].

Ultimately, in AD, the loss of brain cells is severe and irreversible, leading to memory, cognitive, and behavioral problems (Ting et al., 2018) [73]. As the population of individuals living with diabetes increases due to poor diet, lack of exercise, and aging populations, the number of people with brain-related complications is also rising (Verdile et al., 2015) [78]. According to Ficiarà et al. (2025) [23], Alzheimer's is the most common type of dementia worldwide, and when it is combined with diabetes, it becomes an even bigger public-health concern.

Methods

Our aim for the review was to explore the role of chronic hyperglycemia in T2D in promoting oxidative stress, neuroinflammation, AGE formation, and proteinopathies through the polyol pathway and ROS, linked to AD. To this end, we compiled and synthesized existing research from articles retrieved through PubMed, Google Scholar, and Semantic Scholar. The search terms included "hyperglycemia," "polyol pathway," "advanced glycation end-products (AGEs)," "oxidative stress," "neuroinflammation," "amyloid beta," "neurofibrillary tangles," or "Alzheimer's Disease." Abstracts for each article were peer-reviewed for relevance, and then selected studies were grouped by key mechanisms: metabolic pathways (polyol pathway, AGEs, RAGE interaction), vascular dysfunction, oxidative stress markers (ROS and neuroinflammation), and the link between diabetes-related metabolic changes and AD pathology. In summary, this systematic approach helped identify common findings and gaps in the literature, which guided the structure and discussion of the review (Table 1).

Understanding of Diabetes Mellitus and Related Conditions

Overview of Diabetes Mellitus

Diabetes Mellitus is a group of metabolic disorders defined by long-term high blood sugar, also known as chronic hyperglycemia. This condition stems from problems in insulin production and/or function (Banday et al., 2020; Asogwa et al., 2023) [65,22]. There are four primary types of diabetes: Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), gestational diabetes (GDM), and diabetes caused by other factors such as medications, mitochondrial dysfunction, and genetic syndromes (Banday et al., 2020; Ojo et al., 2024; Simkova & Capcarova, 2025) [65,]. Specifically, T1DM is an autoimmune disease in which the body's immune system destroys insulin-producing beta cells in the pancreas, leading to a complete lack of insulin (Szablewski, 2014). Immune-mediated type I diabetes often co-occurs with other autoimmune diseases which can co-occur with other autoimmune diseases such as thyroid disease, Graves', Hashimoto's, or Addison's (American Diabetes Association, 2011).

Table 1: PICO Framework Table.

PICO Element	Inclusion Criteria	Exclusion Criteria
Population	Adult human or animal studies examining adults with Type 2 Diabetes Mellitus, hyperglycemia, or insulin resistance in relation to cognitive decline or AD pathology	Studies only involving Type 1 Diabetes or unrelated neurological conditions (ex., Epilepsy, schizophrenia)
Indicator	Chronic hyperglycemia, insulin resistance, oxidative stress, or polyol pathway activation linked to ad markers (Aβ, tau, neuroinflammation)	Studies not examining glycemic status, metabolic pathways, or those purely focused on cardiovascular complications without cognitive measures
Comparison	Studies that compared diabetic	No control or comparison group;
	vs. non-diabetic groups or stratifief by glucose control levels	case studies without contrasts
Outcomes	Studies that measured brain changes (ex. Neurodegenration, Aβ/tau levels), cognitive outcomes, or oxidative stress biomarkers	Articles not reporting relevant brain or cognitive outcomes (ex. Studies only measuring BMI or insulin levels without neuro data)
Study Design	Peer reviewed original research articles, systematic reviews, or meta analyses focused on biological pathways	Editorals, opinion/commentaries, case studies without empirical methods, non-peer reviewed sources

Conversely, Type 2 diabetes mellitus (T2DM) – the most common form – is caused by insulin resistance and a gradual decline in insulin production. It is often associated with obesity, a sedentary lifestyle, and genetic risk factors (Banday et al., 2020; Asogwa et al., 2023) [65,22]. In cancer survivors, T2DM rarely occurs in isolation and frequently clusters with CVD, obesity, and hypertension, contributing to multimorbidity. At the molecular level, insulin resistance reflects impaired glucose uptake due to dysregulated GLUT4 transport in fat and muscle cells (Ito et al., 2019) [30]. Moreover, obesity-induced inflammation exacerbates this process by releasing pro-inflammatory cytokines and elevating oxidative stress (Iro et al., 2019). These same mechanisms also drive other chronic diseases, explaining why T2DM is a major contributor to multimorbidity. Similarly, GDM refers to hyperglycemia first recognized during pregnancy and usually improves postpartum; however, it confers a long-term increase in T2DM and cardiovascular risk (Banday et al., 2020) [65]. The fourth category, "other specific types," includes diabetes secondary to diseases or exogenous influences such as certain medications (Asogwa et al., 2023) [22].

Overall, although each type has different causes, all share chronic hyperglycemia, which can lead to complications including retinopathy, nephropathy, and CVD (Tiwari, 2014; Ighodaro, 2018; Lei et al., 2024) [74,42]. On a cellular level, hyperglycemia activates the polyol pathway, which increases the formation of ROS (Tiwari, 2014; Lei et al., 2024) [74,42]. Elevated ROS in the setting of depleted antioxidants, particularly glutathione (GSH), causes cellular injury and initiates pro-inflammatory signaling (Tiwari, 2014) [74]. In addition, hyperglycemia-driven mechanisms such as AGE formation, protein kinase C activation, and hexosamine pathway flux further amplify oxidative stress and impair vascular function (Lei et al., 2014) [42].

Consequently, understanding these mechanisms clarifies diabetes' role in neurodegenerative disease and aids in developing effective prevention and treatment strategies (Tiwari, 2014; Ito et al., 2019; Jyotsna et al., 2023) [74,30,34].

Metabolic Syndrome and Related Health Issues

Metabolic syndrome is a group of health problems that increase the risk of T2D and heart disease. Central obesity, insulin resistance, dyslipidemia, and hypertension are core components (Chatterjee & Mudher, 2018) [11]. Specifically, diagnostic checkpoints for Metabolic Syndrome (MetS) include (1) elevated triglycerides, (2) reduced high-density lipoprotein (HDL) levels, (3) increased waist circumference, (4) elevated blood pressure, and (5) impaired fasting glucose (Stanciu et al., 2020; Decourt et al., 2021) [67,16]. Additionally, MetS contributes to brain disorders by affecting systemic and cerebral metabolism (Stanciu et al., 2020; Decourt et al., 2021) [67,16]. Importantly, these metabolic disturbances also impair vascular function and cerebral blood flow, both of which are key predictors of cognitive decline and Alzheimer's disease (AD) (Stanciu et al., 2020; Hooti et al., 2024) [67]. More specifically, chronic hyperglycemia triggers oxidative stress and inflammation (Cioffi et al., 2019; González et al., 2023) [14,26]. Specifically, obesity maintains low-grade inflammation, disrupting adipokines and activating pathways that interfere with insulin function (Rocha, 2011; Ito et al., 2019). Decreased insulin response worsens when oxidative stress reduces GLUT4 transporter activity, further disrupting blood sugar regulation (Ito et al., 2019). Furthermore, metabolic syndrome leads to lipid imbalances–high triglycerides and low HDL levels–which contribute to fatty plaques and impaired blood flow (Stanciu et al., 2020; Decourt et al., 2021). Furthermore, ApoE4 allele exacerbates lipid dysregulation and impairs insulin signaling, particularly in the brain, and it strongly increases AD risk by promoting amyloid-β accumulation, tau pathology, and neuroinflammation (Farmer, 2019). ApoE4 contributes to peripheral insulin resistance and metabolic traits in some mammalian and experimental model studies but appears context dependent (Stanciu et al., 2020). Under hyperglycemic conditions, the polyol pathway is up-regulated; aldose reductase reduces excess glucose to sorbitol, and sorbitol dehydrogenase oxidizes sorbitol to fructose (Sano, 2022). Consequently, enhanced aldose-reductase activity depletes cellular NADPH, impairing glutathione recycling, while sorbitol accumu-

lation imposes osmotic stress. The resulting ROS injures vascular and parenchymal cells and accelerates AGE formation (Kowluru & Chan, 2007; Ito et al., 2019; González et al., 2023). Impaired fasting glucose (IFG) or glucose tolerance (IGT), is strongly associated with metabolic syndrome (Kang, 2005). These conditions raise the risk of diabetes and CVD and indicate that blood sugar problems have already begun to affect the body. Moreover, autoimmune diseases can occur at any age and are influenced by both genetics and environment (American Diabetes Association, 2011). Ongoing inflammation, oxidative stress, and lipid problems lead to neuronal damage and loss (Cioffi et al., 2019; Decourt et al., 2021). As a result, key AD changes–amyloid beta deposits, tau buildup, and cell death–are exacerbated by these metabolic issues (Stanciu et al., 2020). Reduced blood flow further weakens neurons, promoting cognitive decline (Decourt et al., 2021). Therefore, treating metabolic syndrome requires addressing high blood sugar, unhealthy cholesterol, and inflammation together. Because these issues are interconnected, a combined approach may reduce the risk of both diabetes and brain-related complications (Chatterjee & Mudher, 2018; Ito et al., 2019; Stanciu et al., 2020).

Causes and Effects of Hyperglycemia

To begin with, chronic hyperglycemia begins when insulin is not produced in sufficient amounts or does not function effectively (Banday et al., 2020; Ficiarà et al., 2025). Ultimately, this ongoing elevation in blood glucose disrupts normal metabolism and contributes to diabetic complications (Hooti et al., 2024). High blood sugar exacerbates oxidative stress and inflammation by activating the polyol pathway, where excess glucose is converted into sorbitol. In this process, NADPH is consumed, reducing glutathione levels and increasing oxidative damage (Ito et al., 2019; Carter & Bombek, 2022). It also contributes to osmotic stress within cells. Simultaneously, hyperglycemia increases AGE formation, which occurs when glucose binds non-enzymatically to proteins and fats. AGEs accumulate in tissues, alter protein structure, and interact with RAGE, triggering inflammatory signals and further oxidative stress (Ito et al., 2019; Carter & Bombek, 2022).

Another significant issue is the increased production of ROS from the mitochondria, among other sources.. Here, overactive glucose and lipid metabolism create a high NADH/NAD+ ratio, leading to excess ROS and protein and lipid oxidation, closely tied to T2DM progression (Carter & Bombek, 2022). ROS also damage blood vessels, contributing to endothelial dysfunction, hypertension, and chronic inflammation (Ito et al., 2019). In the pancreas, hyperglycemia activates harmful signaling pathways, such as MAPK and NF-κB, leading to beta-cell apoptosis and reduced insulin production (Carter & Bombek, 2022). Likewise, amylin accumulation impairs insulin secretion and may be linked to neurodegeneration (Stanciu et al., 2020). Finally, long-term high blood sugar also causes brain inflammation and oxidative stress, increasing the development of Aβ plaques and tau tangles. Notably, these effects worsen in individuals with the ApoE4 allele (Ito et al., 2019). In metabolic syndrome, oxidative stress is driven by multiple combined factors such as high glucose, abnormal lipids, and hypertension.

Global Prevalence and Societal Impact

Diabetes Mellitus has become a growing global health crisis. Its prevalence has risen rapidly worldwide, driven by lifestyle factors such as diet and physical inactivity. According to recent estimates, about 382 million people live with diabetes globally, and this number expected to reach nearly850 million by mid century (Banday et al., 2020; Hooti et al., 2024). The steepest increases are occurring in low- and middle-income nations, where healthcare systems are already strained (Banday et al., 2020; Hooti et al., 2024). Consequently, diabetes and hyperglycemia cause major complications that increase morbidity and mortality. Cardiovascular disease remains the leading cause of death in this population (Jyotsna et al., 2023). Treatment costs–including hospital care, medications, and long-term management–are extremely high (Hooti et al., 2024; Li et al., 2024). In addition, indirect costs such as loss of productivity and caregiver burden further strain families and health systems.

Diabetes significantly increases the risk of dementia, including AD and like tauopathies (Hooti et al., 2024). Thus, this overlap adds to the global burden of disease and underscores the need for timely screening and intervention. Although rare forms such as neonatal diabetes affect fewer individuals, they present unique diagnostic and treatment challenges (Banday et al., 2020). Genetic traits such as ApoE4 increase vulnerability to diabetes-related brain complications (Hooti et al., 2024). Therefore, public health strategies should prioritize early diabetes screening, lifestyle interventions, and equitable access to care. Coordinated research and policy efforts are essential to reduce the growing burden of diabetes and its neurological complications (Jyotsna et al., 2023; Hooti et al., 2024; Li et al., 2024).

Cognitive Dysfunction and Neurodegenerative Diseases

Overview of Dementia and Neurodegeneration

Neurodegeneration is a progressive, frequently irreversible decline in neuronal integrity that encompasses synaptic dysfunction, loss of structural complexity, and ultimately, cell death (Jellinger, 2010; Dasha et al., 2025). Collectively, this pathological cascade contributes to disorders such as AD, PD, HD, ALS, and dementias including frontotemporal and Lewy body dementia (Sweeney et al., 2017; Dasha et al., 2025).

As neuronal networks falter, it's common for dementia patients to show subtle memory and executive function impairments and later progress to language, visuospatial, and motor deficits (Hottman et al., 2014; Katsuno et al., 2018; Dasha et al., 2025). Clinically, dementia describes cognitive decline severe enough to interfere with daily life and results from various neurodegenerative processes (Ravona-Springer et al., 2014; Fymat, 2019). Symptoms include memory loss, language problems, and difficulty performing complex tasks; clinicians often assess severity using the Clinical Dementia Rating (CDR) scale (Ravona-Springer et al., 2014). At the molecular level, the pathophysiology of neurodegeneration involves toxic protein aggregates.

In AD, soluble amyloid-beta (Aβ) oligomers disrupt synaptic communication and drive synapse loss of function (Meneses et al., 2021). Brain microbleeds can exacerbate AD pathology by releasing hemoglobin and iron, which promote oxidative stress and may foster Aβ aggregation and plaque-associated toxicity (Ficiarà et al., 2025). Excess reactive oxygen species (ROS) overwhelm antioxidant defenses and damage cellular macromolecules, while activated microglia and astrocytes release pro-inflammatory cytokines that perpetuate neuronal injury (Johnstone et al., 1998; Dasha et al., 2025). Furthermore, damage-associated molecular patterns such as HMGB1 bind to RAGE and TLR4, intensifying inflammation and cognitive decline (Nakahira et al., 2015; S et al., 2024).

Key Characteristics and Progression of Alzheimer's Disease

Amyloid-beta (Aβ) Accumulation and Plaque Formation

Aβ peptides, derived from amyloid precursor protein (APP) via β- and γ-secretases, accumulate into insoluble fibrils that form plaques (Takahashi et al., 2017). Genetically, autosomal-dominant mutations in APP-prone Aβ species, while the presenilin genes and the ApoE4 allele impair Aβ clearance and promote plaque deposition (Su et al., 2023). Aβ contributes to ROS production, creating a damaging feedback loop (Hooti et al., 2024). In diabetes, hyperglycemia increases AGE production; in turn, AGEs bind to Aβ and enhance aggregation while activating RAGE-mediated oxidative pathways (S et al., 2024). This mechanistic overlap links metabolic and neurodegenerative processes (Stanciu et al., 2020). Aβ accumulation disrupts neuronal signaling and activates microglia, driving neuroinflammation that contributes to cognitive decline (Hooti et al., 2024). Accordingly, the "amyloid hypothesis" proposes Aβ buildup as a central driver of AD (Stanciu et al., 2020).

Tau Proteins and Neurofibrillary Tangle (NFT) Development

Tau pathology involves abnormal hyperphosphorylation, causing tau to detach from microtubules and form neurofibrillary tangles (NFTs) (Kim et al., 2015). These tangles correlate with memory and thinking problems (Hooti et al., 2024; S et al., 2024). Moreover, reduced insulin activity increases GSK3β action, enhancing tau phosphorylation (Ahn et al., 2019; Gonçalves et al., 2019). Inflammation and oxidative stress further accelerate tau aggregation (Chatterjee & Mudher, 2018). Notably, ApoE4 increases the risk and aggressiveness of both amyloid and tau pathology (DeTure & Dickson, 2019).

Neuronal Loss and Synaptic Breakdown

Neuronal and synaptic loss underlie cortical and hippocampal atrophy, leading to memory and cognitive decline (Chatterjee & Mudher, 2018; Hooti et al., 2024). Mechanistically, Aβ plaques impair neurotransmission, and tau tangles disrupt cytoskeletal transport. Mitochondrial dysfunction and loss of coenzyme Q10 reduce oxidative-stress tolerance (Abdel Moneim, 2015). Consequently, synaptic loss often precedes neuronal death, serving as an early indicator of cognitive decline.

Early Symptoms and Disease Progression

During prodromal AD, patients exhibit mild memory and attention deficits that gradually interfere with independence. Early symptoms vary by brain region affected (DeTure & Dickson, 2019; Hooti et al., 2024). Typically, Aβ accumulation often precedes NFT formation; together they impair neuronal communication and memory (Decourt et al., 2021). In diabetes, chronic hyperglycemia worsens these changes via oxidative stress and AGE buildup (Abdel Moneim, 2015; Ito et al., 2019).

Insulin resistance disrupts neuronal signaling essential for cognition (Stanciu et al., 2020). Elevated ROS damages cerebral vasculature, reducing blood flow and causing micro- and macrovascular injury linked to cognitive deficits (Ito et al., 2019; Asogwa et al., 2023). These complications impair the blood-brain barrier and increase neuronal vulnerability. Furthermore, ApoE4 carriers face faster decline, and chronic inflammation with high IL-6 and IL-8 exacerbates pathology (Su et al., 2023).

Connections Between Hyperglycemia and Neurodegeneration

Key Cellular and Molecular Pathways

Polyol Pathway and Oxidative Stress

The polyol pathway is upregulated during chronic hyperglycemia. Aldose reductase converts excess glucose to sorbitol, using NADPH, and sorbitol dehydrogenase oxidizes it to fructose (Black, 2022; Yonamine et al., 2023). Neurons and glia primarily rely on insulin-independent glucose transport, making the CNS particularly exposed to high glucose. NADPH consumption in the polypol pathway limits glutathione regeneration, weakening antioxidant defenses. Fructose is highly glycating and accelerates AGE formation, making the CNS vulnerable. NADPH depletion reduces glutathione regeneration, weakening antioxidant defenses (Obrosova, 2005). Sorbitol accumulation causes osmotic stress, and fructose promotes AGE formation, degrading synaptic and neuronal function (Black, 2022). Hyperglycemia-driven oxidative stress, to which the polyol pathway contributes, also triggers PKC and the hexosamine pathway, amplifying AGE production and glial dysfunction (Puspa-rajah et al., 2016; Black, 2022).

Advanced Glycation End-Products (AGEs) and Inflammation

AGEs form when sugars combine with proteins, fats, or DNA without enzymes (Twarda-Clapa et al., 2022). Chronic hyperglycemia accelerates this process, leading to accumulation in tissues including the brain (Ullah et al., 2019). When AGEs bind to RAGE on neurons, glia, and endothelium, NF-κB activation increases oxidative stress and inflammation (Pugazhenthi et al., 2017). Consequently, this loop elevates BACE1 levels and promotes Aβ and tau aggregation (Verdile et al., 2015). ROS amplify AGE formation, and AGEs further induce ROS, sustaining damage (Chawla et al., 2016). Additionally, AGE-RAGE signaling triggers cytokine release (TNF-α, interleukins) and microglial activation, causing synaptic

loss and neuronal death (Su et al., 2023; Ficiarà et al., 2025). It also alters proteostasis and weakens the blood-brain barrier, increasing permeability to inflammatory mediators (Ullah et al., 2019). Collectively, these findings indicate that AGE-related oxidative stress contributes to diabetic complications beyond the brain, including nephropathy and retinopathy (Chawla et al., 2016).

Reactive Oxygen Species (ROS) and Antioxidant Systems

Sources and Impacts of ROS

ROS such as superoxide (O2·-), hydrogen peroxide (H2O2), and hydroxyl radicals (·OH) are produced mainly by the mitochondrial electron transport chain. Hydrogen peroxide crosses membranes and, in the presence of Fe^{2+}, forms hydroxyl radicals via Fenton chemistry–the most cytotoxic species (Markesbery & Lovell, 2007; Das et al., 2014; Zang et al., 2019). Polyol-pathway activity and AGE-RAGE signaling both enhance ROS generation while depleting NADPH and glutathione (Verdile et al., 2015; Black, 2022). As a result, excess ROS damage membranes, proteins, and DNA, impairing mitochondria and synapses. Elevated oxidation markers are found in AD brains (Kim et al., 2015). At physiological levels ROS act as signaling molecules, but chronic overproduction overwhelms antioxidant systems and promotes apoptotic and necrotic cell death (Moreira et al., 2006). In diabetes, persistent oxidative imbalance interlocks with Aβ aggregation and tau hyperphosphorylation, reinforcing AD-like pathology (Cioffa et al., 2019). Moreover, genetic inheritance of the ApoE4 allele is associated with increased oxidative damage and reduced antioxidant capacity in brain tissue, further heightening vulnerability to ROS-mediated injury (Klimontov et al., 2021).

Impaired Antioxidant Defense Mechanisms

Brain antioxidant systems–including GSH, CAT, GPX, SOD and vitamin E–maintain redox balance (Cioffa et al., 2019). In diabetes, these defenses decline; neurons, which do not regenerate easily, become highly vulnerable (Ramli et al., 2020). Furthermore, polyol-pathway NADPH loss and mitochondrial dysfunction weaken antioxidant regeneration. Vitamin E depletion increases lipid peroxidation (González et al., 2023). With aging, enzyme activity further decreases, compounding oxidative stress (Ramli et al., 2020; Pires & Rego, 2023). As a result, inflammation activates ROS-producing enzymes, reinforcing the oxidative-inflammatory cycle (Verdile et al., 2015).

Inflammatory and Immune Responses

Chronic hyperglycemia activates multiple inflammatory pathways, including PKC, the hexosamine pathway, and AGE formation, which in turn, converge to increase ROS production and drive activation of pro-inflammatory macrophages (Black, 2022). Inflammation in the diabetic brain is sustained by cytokine dysregulation and endothelial dysfunction, which are closely linked to oxidative stress and vascular injury,

respectively (Klimontov et al., 2021). PKC activation upregulates TGF-β and NF-κB signaling, providing a direct molecular link to oxidative stress to inflammation (Wu et al., 2014). In AD, neuroinflammation tracks closely with Aβ plaques and tau aggregates; specifically, microglial and astrocyte activation releases IL-1β, TNF-α, and other cytokines that drive neuronal death (Chatterjee & Mudher, 2018). Moreover, the gut-brain axis integrates context-dependence elements, illustrated in microbiota dysbiosis enhancement of neuroinflammation (S et al., 2024). Some animal studies suggest tau damage may progress independently of microglial activation (Goalstone & Pugazhenthi, 2016). PGE_2 and related prostaglandins can be either protective or harmful depending on context (Black, 2022). Mapping these interactions, from hyperglycemia and oxidative stress to immune activation, vascular dysfunction, and tau-driven Aβ pathology, may improve understanding of inflammatory progression (Kwakowsky et al., 2023).

Genetic, Epigenetic, and Environmental Risk Factors

Genetic Risk Factors

Apolipoprotein E (APOE) variants strongly influence late-onset AD risk. The ApoE4 allele increases susceptibility and lowers onset age (Strittmatter et al., 1993; Corder et al., 1993). Mechanistically, ApoE4 promotes Aβ aggregation, impairs clearance, and is associated with oligomeric tau pathology (Cioffia et al., 2019; Decourt et al., 2021). ApoE4 also disrupts lipid transport and inflammatory control, making the brain less resilient (Cioffia et al., 2019). Importantly, ApoE4 is a risk factor associated with chronic hyperglycemia and oxidative stress, which compound metabolic injury (Black, 2022). However, ApoE4 alone does not determine disease; other genes, age, sex, and cardiovascular or metabolic conditions contribute (Banday et al., 2020; S et al., 2024). Most T2DM and AD cases arise from multiple gene-environment interactions.

Epigenetic Changes Triggered by Hyperglycemia

Beyond genetic factors, epigenetic modifications –DNA methylation, histone changes, and non-coding RNA shifts–link metabolism to gene regulation (Kowluru & Mohammad, 2022). Specifically, transient hyperglycemia can cause persistent pro-inflammatory gene activation, known as "metabolic memory" (El-Osta et al., 2008). These glucose-driven epigenetic marks are well documented in vascular, renal, and retinal tissues, and emerging data indicate that similar mechanisms contribute to CNS complications (Klimontov et al., 2021). Experimental models show that oxidative stress remodel chromatin and upregulate BACE1 expression, thereby fostering Aβ accumulation (Cioffi et al., 2019). Additionally, environmental factors such as diet or pollutants also modify the epigenome via oxidative and inflammatory pathways (Tiwari, 2014; Ullah et al., 2019).

Environmental and Lifestyle Influences

In parallel with molecular factors, exposure to toxins — such as heavy metals, pesticides, cigarette smoke, polychlorinated biphenyls (PCBs), and arsenic — disrupts mitochondrial function and elevates ROS, thereby driving inflammatory stress in the brain (Decourt et al., 2021; Prakash et al., 2016). Across in vitro and in vivo models, toxin-elicited oxidative stress in linked with accelerated aggregation of pathological protein species, while chronic exposure can also disrupt blood-brain barrier integrity. Consequently, oxida-

tive stress and deregulated signaling accelerate Aβ accumulation, which interacts with overactive kinases, leading to tau aggregation, neurofibrillary tangles, and, eventually, apoptosis (Lyu et al., 2024; Ficiarà et al., 2025). Long-term exposure also damages the blood-brain barrier. Conversely, lifestyle factors such as physical inactivity and poor diet are associated with reduced antioxidant defenses, and higher systemic oxidative stress, whereas healthier behaviors, including regular physical exercise, improved diet quality and reduced exposure to environmental toxicants, enhance antioxidant capacity and are associated with lower dementia risk at the population level (Su et al., 2023; Decourt et al., 2021).

Systems-Level Interactions Between Diabetes and Neurodegeneration

Interaction Among Metabolic, Vascular, and Neural Systems

Chronic hyperglycemia initiates metabolic cascades that affect neurons and blood vessels. Polyol-pathway activation depletes NADPH and impairs glutathione blood vessles, thereby increasing oxidative stress (Yan, 2014). Meanwhile, AGEs bind RAGE on neural and vascular cells, triggering ROS production and pro-inflammatory signaling (Black, 2022; González et al., 2023). Within the context of diabetes-related vascular dysfunction, these processes limit oxygen and nutrient delivery and amplify neuroinflammation (Hooti et al., 2024). Consequently, oxidative stress and inflammation reinforce each other, contributing to neuronal loss (S et al., 2024). PKC activation and DAG accumulation increase vessel permeability and play a role in microvascular leakage and impaired clearance of metabolic by-products and waste (Black, 2022). Furthermore, metabolic defects in diabetes–poor insulin signaling and mitochondrial impairment–intensify Aβ and tau accumulation (Ting et al., 2018; Pandiyan et al., 2024). Genetic risk factors such as ApoE4 further sensitize individuals to these insults.

Vascular Dysfunction and Its Role in Cognitive Decline

Vascular dysfunction contributes heavily to cognitive decline. Chronic hyperglycemia damages vessels, reduces cerebral blood flow, and weakens the blood-brain barrier (Carter & Bombek, 2022). Moreover, iron accumulation and oxidative stress worsen microvascular injury, linking AD and vascular dementia (Ficiarà et al., 2025). For instance, microstrokes and atherosclerosis compound damage, while AGEs and RAGE activation intensify oxidative stress (Ullah et al., 2019). Consequently, BBB breakdown disrupts Aβ clearance and allows peripheral inflammatory mediators and other solutes to enter the brain, contributing to waste accumulation and neuroinflammation. Altered heme-oxygenase-1 levels correlate with inflammation and tau pathology (Ficiarà et al., 2025). Ultimately, reduced cerebral perfusion impairs neuronal connectivity, producing hallmark dementia symptoms (Hooti et al., 2024).

Peripheral Neuropathy and Central Nervous System Effects

Peripheral neuropathy and CNS degeneration share diabetic origins. Long-term metabolic imbalance and oxidative stress damage peripheral nerves, causing axonal loss and demyelination (Chawla et al., 2016). In addition, mitochondrial ROS overproduction disrupts axonal transport; inadequate mitophagy perpetuates injury (Dasha et al., 2025). Insulin signaling in the brain–vital for memory and learning–is impaired, likely contributing to mild cognitive impairment and AD (Stanciu et al., 2020; Hooti et al., 2024). Likewise, defective autophagy and lysosomal clearance foster Aβ and tau accumulation (Chatterjee & Mudher, 2018). Cerebrovascular pathology interacts with neurodegeneration to amplify decline (DeTure & Dickson, 2019). Finally, genetic factors affecting lipid handling and inflammation further increase vulnerability (Banday et al., 2020).

Conclusion

Chronic hyperglycemia initiates a cascade of biochemical disruptions that extend far beyond glucose metabolism. Through activation of the polyol pathway, depletion of NADPH, formation of AGEs, and excessive ROS production, diabetes creates a persistent state of oxidative stress and inflammation. Consequently, these processes damage neurons, impair vascular integrity, and accelerate the accumulation of amyloid-beta and tau, key hallmarks of Alzheimer's disease. Therefore, the convergence of metabolic and neurodegenerative mechanisms underscores the importance of early glucose control and antioxidant protection. Moreover, targeting shared pathways–such as AGE-RAGE signaling and mitochondrial dysfunction–offers potential therapeutic value. Future research should further explore how genetic factors like ApoE4 and epigenetic changes modulate this relationship, paving the way for integrated prevention and treatment strategies that address both metabolic and cognitive decline. Future research should clarify how genetic factors like ApoE4 and epigenetic modifications shape the interplay, enabling integrated prevention and treatment strategies that simultaneously address metabolic, vascular and cognitive decline. Overall, dissecting the biochemical overlap between diabetes and neurodegeneration not only advances insight into disease mechanisms but also reinforces the need for holistic clinical management of subjects at metabolic and neurological risk.

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Conflict of Interest

No Conflict of interest.

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