Metabolic Dysfunction and Neurodegeneration: Pharmacological Strategies Targeting Diabetes-Associated Alzheimer's disease

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Abstract

Background: Alzheimer's disease represents a leading cause of dementia worldwide and is increasingly recognized as a complex, multifactorial disorder extending beyond classical amyloid and tau pathologies. Growing epidemiological and mechanistic evidence highlights type 2 diabetes mellitus as a major risk factor for cognitive decline and Alzheimer's disease, giving rise to the concept of diabetes-associated neurodegeneration. Metabolic dysfunction, characterized by insulin resistance, chronic hyperglycemia, dyslipidemia, and systemic inflammation, contributes to neuronal vulnerability through impaired brain insulin signaling, mitochondrial dysfunction, oxidative stress, and neuroinflammatory cascades. These overlapping pathological mechanisms suggest that metabolic disorders not only coexist with neurodegeneration but actively modulate its onset, progression, and severity.

Aim: This review aims to critically evaluate the mechanistic links between metabolic dysfunction and Alzheimer's disease from a clinical pharmacology perspective, with particular emphasis on diabetes-associated cognitive impairment. It explores key molecular pathways connecting peripheral metabolic disturbances to central nervous system pathology and examines pharmacological strategies capable of modulating these shared mechanisms. By synthesizing evidence from experimental, translational, and clinical studies, this review seeks to identify therapeutic approaches that target metabolic, inflammatory, oxidative, and neurodegenerative pathways simultaneously.

Conclusion: Accumulating data support the concept that Alzheimer's disease associated with metabolic dysfunction represents a distinct and therapeutically relevant subtype of neurodegeneration. Pharmacological interventions originally developed for metabolic disorders have demonstrated pleiotropic effects on neuroinflammation, synaptic plasticity, oxidative stress, and neuronal survival, suggesting potential benefits beyond glycemic control. However, translational gaps remain regarding optimal timing, patient selection, and long-term cognitive outcomes. A deeper understanding of the metabolic–neurodegenerative interface may facilitate the development of disease-modifying strategies that address both systemic metabolic dysregulation and central neurodegenerative processes. Integrating clinical pharmacology with neurobiology offers a promising framework for advancing precision medicine approaches in diabetes-associated Alzheimer's disease.

Keywords: *Metabolic Dysfunction , Neurodegeneration, Diabetes, Alzheimer's disease*

Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and represents a major public health challenge due to its progressive nature, lack of curative therapy, and growing prevalence in aging populations. Clinically, AD is characterized by gradual impairment of memory, executive function, and behavior, while neuropathologically it is defined by amyloid-β plaque deposition, neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic loss, and neuronal degeneration. Although advancing age is the strongest non-modifiable risk factor, increasing attention has been directed toward systemic conditions that modify disease risk and progression. Among these,

type 2 diabetes mellitus (T2DM) has emerged as a significant and independent risk factor for cognitive decline and AD, with large cohort studies demonstrating higher dementia incidence and accelerated cognitive deterioration in diabetic populations compared with non-diabetic individuals [1][2].

The mechanistic relationship between T2DM and AD extends beyond shared epidemiological associations and reflects overlapping molecular and cellular pathways. Chronic insulin resistance, a defining feature of T2DM, is increasingly recognized within the central nervous system, where insulin plays a critical role in neuronal survival, synaptic plasticity, and memory formation. Impaired brain insulin signaling disrupts glucose utilization, alters neurotransmitter regulation, and promotes amyloidogenic processing of amyloid precursor protein, leading to increased amyloid-β accumulation. In parallel, insulin resistance has been linked to enhanced tau phosphorylation through dysregulation of kinase and phosphatase activity, thereby contributing directly to neurofibrillary pathology [3][4]. These abnormalities are compounded by mitochondrial dysfunction and reduced cerebral energy metabolism, which further sensitize neurons to degeneration.

In addition to insulin resistance, metabolic dysfunction in T2DM is associated with chronic low-grade inflammation, oxidative stress, and vascular impairment, all of which play central roles in the pathogenesis of AD. Systemic inflammation promotes microglial activation and neuroinflammatory cascades within the brain, while sustained hyperglycemia increases reactive oxygen species production and impairs antioxidant defenses. Moreover, diabetes-related endothelial dysfunction and cerebrovascular disease compromise cerebral perfusion and blood–brain barrier integrity, exacerbating neuronal injury and facilitating neurotoxic protein accumulation. Despite extensive experimental evidence supporting these links, significant gaps remain in translating mechanistic insights into effective therapeutic strategies. Understanding how pharmacological modulation of metabolic pathways influences neurodegenerative processes is therefore essential for developing targeted interventions for diabetes-associated Alzheimer’s disease [5][6].

Pathophysiological Links Between Metabolic Dysfunction and Alzheimer’s Disease

Metabolic dysfunction plays a central role in shaping the neurobiological environment that predisposes individuals with type 2 diabetes mellitus to Alzheimer’s disease. One of the earliest and most critical alterations involves impaired cerebral glucose metabolism, which has been consistently demonstrated in neuroimaging studies of patients with insulin resistance and early Alzheimer’s pathology. Neurons are highly energy-dependent cells, and reduced glucose uptake and utilization lead to synaptic failure, impaired neurotransmission, and eventual neuronal loss. Positron emission tomography studies have shown that cerebral hypometabolism precedes clinical cognitive decline, suggesting that metabolic impairment is not merely a consequence but a driver of neurodegeneration in diabetes-associated Alzheimer’s disease [7].

Insulin signaling within the brain exerts profound effects on neuronal growth, synaptic plasticity, and memory consolidation. Under physiological conditions, insulin modulates long-term potentiation, regulates neurotransmitter receptor trafficking, and supports neuronal survival pathways. In states of systemic insulin resistance, these neuroprotective functions are compromised due to downregulation of insulin receptors and post-receptor signaling defects in the brain. Impaired activation of downstream pathways such as phosphoinositide 3-kinase and protein kinase B leads to increased activity of glycogen synthase kinase-3β, a key enzyme implicated in tau hyperphosphorylation. This molecular convergence links metabolic dysregulation directly to the formation of neurofibrillary tangles, a pathological hallmark of Alzheimer’s disease [8][9].

Oxidative stress represents another major mechanistic bridge between metabolic dysfunction and neurodegeneration. Chronic hyperglycemia promotes excessive production of reactive oxygen species through mitochondrial overload, advanced glycation end-product formation, and activation of nicotinamide adenine dinucleotide phosphate oxidases. Neuronal cells are particularly vulnerable to oxidative damage due to their high metabolic rate and limited regenerative capacity. Accumulation of oxidative damage to lipids, proteins, and nucleic acids disrupts synaptic integrity and accelerates neuronal apoptosis. In Alzheimer’s disease, oxidative stress has been shown to exacerbate amyloid-β

aggregation and impair proteasomal and autophagic clearance mechanisms, further amplifying neurotoxic protein accumulation in the diabetic brain [10].

Neuroinflammation constitutes a critical downstream consequence of metabolic imbalance and a major contributor to progressive neurodegeneration. Peripheral metabolic inflammation associated with obesity and T2DM facilitates the release of pro-inflammatory cytokines that can access the central nervous system through a compromised blood–brain barrier. Within the brain, activated microglia and astrocytes adopt a pro-inflammatory phenotype, releasing cytokines, chemokines, and reactive oxygen species that impair synaptic function and neuronal viability. Sustained neuroinflammation not only accelerates amyloid-β deposition and tau pathology but also interferes with insulin signaling pathways in a feed-forward manner. This bidirectional interaction between metabolic dysfunction and neuroinflammation underscores the complexity of diabetes-associated Alzheimer's disease and highlights the need for therapeutic strategies targeting multiple interconnected pathways [11][12].

Role of Mitochondrial Dysfunction and Energetic Failure in Diabetes-Associated Neurodegeneration

Mitochondrial dysfunction represents a pivotal pathological mechanism linking metabolic disorders to neurodegenerative processes in Alzheimer's disease. In the context of type 2 diabetes mellitus, chronic insulin resistance and hyperglycemia disrupt mitochondrial dynamics, biogenesis, and respiratory efficiency within neuronal cells. Impaired oxidative phosphorylation reduces adenosine triphosphate production, compromising synaptic transmission and axonal transport, both of which are energy-intensive processes essential for cognitive function. Neuroimaging and postmortem studies have demonstrated reduced mitochondrial enzyme activity and altered mitochondrial morphology in brains affected by Alzheimer's disease, supporting the concept that energetic failure precedes overt neuronal loss in metabolically compromised individuals [13].

Excessive production of reactive oxygen species secondary to mitochondrial dysfunction further amplifies neuronal injury in diabetes-associated Alzheimer's disease. Under physiological conditions, mitochondrial respiration is tightly regulated to balance energy production and oxidative stress. However, in hyperglycemic states, increased electron leakage from the electron transport chain leads to oxidative damage of mitochondrial DNA, lipids, and proteins. This damage impairs mitochondrial integrity and perpetuates a vicious cycle of declining respiratory capacity and escalating oxidative stress. In Alzheimer's pathology, oxidative modification of mitochondrial components has been closely associated with amyloid-β accumulation, which itself can localize to mitochondria and disrupt respiratory chain complexes, thereby exacerbating neuronal energy deficits [14].

Mitochondrial dysfunction also interferes with calcium homeostasis, a critical regulator of neuronal excitability and survival. Insulin resistance and oxidative stress impair mitochondrial calcium buffering capacity, resulting in cytosolic calcium overload and activation of calcium-dependent proteases and apoptotic pathways. Dysregulated calcium signaling contributes to synaptic dysfunction, dendritic spine loss, and neuronal apoptosis, all of which are prominent features of Alzheimer's disease. Furthermore, altered mitochondrial permeability transition pore activity has been implicated in the release of pro-apoptotic factors, linking metabolic stress directly to programmed neuronal death in diabetes-associated neurodegeneration [15].

Beyond neuronal cells, mitochondrial impairment affects glial function and neurovascular coupling, further contributing to cognitive decline. Astrocytes play a critical role in supporting neuronal metabolism by regulating glucose uptake and lactate shuttling, while endothelial cell mitochondria are essential for maintaining blood–brain barrier integrity. Metabolic dysfunction disrupts these supportive roles, leading to reduced metabolic flexibility and increased vulnerability to neurotoxic insults. Collectively, these findings highlight mitochondrial dysfunction as a central integrator of metabolic and neurodegenerative pathology and underscore its importance as a therapeutic target in diabetes-associated Alzheimer's disease [16].

Neurovascular Dysfunction and Blood–Brain Barrier Alterations in Metabolic-Associated Alzheimer's Disease

Neurovascular dysfunction is increasingly recognized as a critical mediator linking metabolic disorders to the development and progression of Alzheimer's disease. Type 2 diabetes mellitus is associated with endothelial dysfunction, impaired nitric oxide bioavailability, and chronic vascular inflammation, all of which compromise cerebral blood flow regulation. Adequate cerebral perfusion is essential for maintaining neuronal metabolism and waste clearance, and sustained reductions in blood flow contribute to hypoxia, glucose deprivation, and accumulation of neurotoxic metabolites. Epidemiological and imaging studies have demonstrated that individuals with diabetes exhibit accelerated cerebral small vessel disease and reduced cerebrovascular reactivity, which correlate with cognitive impairment and increased Alzheimer's disease risk [17].

The blood–brain barrier (BBB) serves as a highly selective interface that protects the central nervous system from circulating toxins while regulating the transport of nutrients and signaling molecules. Metabolic dysfunction disrupts BBB integrity through multiple mechanisms, including oxidative stress, advanced glycation end-product accumulation, and inflammatory cytokine signaling. Hyperglycemia-induced endothelial injury alters tight junction protein expression, leading to increased BBB permeability. This breakdown facilitates the entry of peripheral inflammatory mediators and potentially neurotoxic substances into the brain parenchyma, thereby amplifying neuroinflammatory responses and neuronal damage associated with Alzheimer's pathology [18].

BBB dysfunction also interferes with amyloid-β homeostasis, a key pathological feature of Alzheimer's disease. Under normal conditions, amyloid-β is actively transported across the BBB for clearance from the brain into the peripheral circulation. Diabetes-related vascular damage impairs the expression and function of transporters involved in amyloid-β efflux, resulting in its accumulation within the brain. Concurrently, increased BBB permeability may enhance the influx of circulating amyloidogenic peptides and inflammatory factors, creating an environment that favors plaque formation and synaptic toxicity. These vascular-mediated alterations provide a mechanistic explanation for the accelerated amyloid burden observed in metabolically compromised individuals [19].

In addition to endothelial cells, pericytes and astrocytic end-feet play essential roles in maintaining BBB stability and neurovascular coupling. Metabolic stress adversely affects these supporting cells, leading to impaired communication between neurons and the vascular system. Astrocytic dysfunction disrupts metabolic support to neurons, while pericyte loss has been linked to capillary degeneration and reduced cerebral perfusion. Together, these changes contribute to a progressive decline in neurovascular integrity and cognitive function. Targeting neurovascular health therefore represents a promising therapeutic avenue for mitigating the impact of metabolic dysfunction on Alzheimer's disease progression [20].

Pharmacological Modulation of Metabolic Pathways in Diabetes-Associated Alzheimer's Disease

From a clinical pharmacology standpoint, the most pragmatic strategy for diabetes-associated Alzheimer's disease is to target *shared upstream drivers*—insulin resistance, impaired energy signaling, oxidative stress, and chronic inflammation—rather than focusing exclusively on amyloid or tau. Among glucose-lowering therapies, agents that improve insulin sensitivity and reduce systemic inflammatory tone have attracted interest because they may indirectly stabilize neurovascular function, reduce microglial activation, and improve neuronal metabolic resilience. However, the evidence base remains mixed, with benefits often clearer in observational datasets than in randomized cognitive endpoints, highlighting the need to interpret outcomes in light of confounding by indication, duration of exposure, and baseline cognitive stage. [21]

Biguanides have been repeatedly examined because they influence hepatic glucose production, insulin sensitivity, and cellular energy sensing pathways that overlap with neuronal stress signaling. Recent evidence syntheses suggest that use of this class is often associated with *lower dementia risk* in people with diabetes, though heterogeneity exists across study designs, populations, and comparator groups. Clinically, this raises a key translational question: whether apparent neuroprotection reflects direct central effects, improved vascular/metabolic control, or bias related to patient selection and treatment duration. These uncertainties are central when designing future trials that aim to detect disease-modifying cognitive outcomes rather than metabolic surrogate endpoints. [21]

A more direct approach has been to augment central insulin signaling through intranasal delivery to bypass systemic hypoglycemia risk. While early mechanistic rationale was strong—given insulin's roles in synaptic plasticity and neuronal survival—large randomized clinical data have not shown consistent cognitive or functional benefits over placebo, and trial interpretation has been complicated by device and delivery variability. From a pharmacology perspective, this underscores how *route, formulation, and device performance* can determine CNS target engagement, even when the biological hypothesis is compelling. Accordingly, intranasal insulin remains investigational, and its future depends on standardized delivery platforms and biomarker-guided patient stratification. [22]

Incretin-based therapies, particularly those enhancing glucagon-like peptide-1 receptor signaling, have gained major attention due to pleiotropic actions that may modulate neuroinflammation, mitochondrial stress responses, and synaptic function while also improving cardiometabolic health. Clinical evidence to date suggests that, despite promising mechanistic signals and favorable metabolic effects, consistent improvements in core Alzheimer biomarkers or cognition have not been reliably demonstrated across human studies. This gap may reflect insufficient CNS exposure in some contexts, suboptimal treatment timing (too late in established pathology), or the need for combination strategies targeting multiple pathways simultaneously. As a result, the class remains a leading repurposing candidate, but the current clinical signal is best viewed as *hypothesis-generating rather than practice-changing*. [23]

Sodium–glucose cotransporter-2 inhibitors have emerged as a particularly interesting class because of robust cardiovascular and renal benefits, alongside observational signals suggesting lower incidence of dementia compared with some other glucose-lowering therapies. A large population-based cohort analysis reported a significantly reduced risk of dementia outcomes among initiators of this class versus an active comparator, supporting the possibility that vascular and metabolic risk modification translates into brain protection. Nevertheless, these data are observational and cannot establish causality; clinical pharmacology priorities now include defining whether benefits are mediated primarily through cardiometabolic de-risking, ketone/energetic shifts, reduced inflammation, or neurovascular mechanisms, and then testing these pathways in randomized cognitive and biomarker-driven designs. [24]

Thiazolidinediones and lipid-lowering therapies illustrate the broader lesson that mechanistic plausibility does not guarantee clinical efficacy. A large prevention-oriented trial of a peroxisome proliferator–activated receptor-γ agonist did not delay the onset of mild cognitive impairment due to Alzheimer pathology, despite earlier rationale centered on insulin sensitization and anti-inflammatory effects. In parallel, large observational meta-analytic data suggest an association between statin exposure and reduced dementia risk, but confounding and indication bias remain key limitations, and randomized evidence for Alzheimer-specific benefit is not definitive. Together, these examples reinforce the importance of matching pharmacological mechanism to disease stage, optimizing exposure duration, and using biomarker endpoints to confirm target engagement and biological effect. [25][26]

Anti-inflammatory and Antioxidant Pharmacological Strategies at the Metabolic–Neurodegenerative Interface

Chronic low-grade inflammation is a shared biological signature of type 2 diabetes mellitus and Alzheimer's disease, and it plausibly amplifies neurodegeneration through sustained activation of innate immune pathways. In the metabolically stressed brain, microglia can transition toward a pro-inflammatory phenotype that increases cytokine release, oxidative injury, and synaptic dysfunction, creating a feed-forward loop that further worsens insulin signaling and neuronal resilience. Among inflammatory mechanisms, inflammasome activation—particularly NLRP3—has attracted attention because it links metabolic danger signals, amyloid-β and tau-associated stress, and downstream IL-1β/IL-18 signaling that can propagate neuroinflammation and neuronal injury. This framework supports targeting inflammatory "hubs" rather than single downstream mediators, especially in diabetes-associated neurodegeneration where peripheral inflammation may repeatedly "prime" the brain immune milieu. [27]

Oxidative stress represents another major intersection between metabolic dysfunction and

neurodegenerative pathology, with hyperglycemia accelerating reactive oxygen species generation and promoting formation of advanced glycation end products (AGEs). AGE accumulation can intensify oxidative injury and inflammation via receptor-mediated signaling (AGE–RAGE axis), while also contributing to vascular dysfunction and impaired clearance of neurotoxic proteins. Clinically, this suggests that antioxidant and antiglycation strategies may be most useful when implemented early—before irreversible synaptic loss—yet the challenge has been translating broad "antioxidant" concepts into therapies with demonstrable CNS target engagement and clinically meaningful outcomes. Mechanistically grounded approaches that focus on specific oxidative–inflammatory signaling axes (rather than nonspecific supplementation) appear more promising, particularly when aligned with biomarkers of oxidative injury and vascular compromise in diabetes. [28]

Non-steroidal anti-inflammatory drugs (NSAIDs) provide a cautionary example of how epidemiologic signals do not necessarily translate into preventive efficacy in Alzheimer's disease. In the Alzheimer's Disease Anti-inflammatory Prevention Trial and its follow-up analyses, treatment arms did not show an overall reduction in incident Alzheimer's disease compared with placebo, and cognitive outcomes did not improve; this reinforced concerns that timing, patient selection, and mechanism specificity are critical. From a pharmacology lens, NSAIDs may be ineffective once neuroinflammation is already established or may not adequately modulate the relevant central inflammatory networks driving disease in metabolically vulnerable populations. These findings have pushed the field toward more targeted immunomodulatory strategies rather than broad cyclooxygenase inhibition for Alzheimer prevention. [29]

Antioxidant approaches have also produced mixed results, but some controlled clinical evidence suggests possible functional benefits in established Alzheimer's disease with high-dose alpha-tocopherol (vitamin E). In a randomized trial in mild-to-moderate Alzheimer's disease, alpha-tocopherol was associated with slower functional decline compared with placebo, while combination therapy with a standard symptomatic agent did not show additive benefit. Clinically, these data are best interpreted as a signal that oxidative injury may be therapeutically modifiable in some patients, but they do not establish disease modification, and careful consideration of safety, comorbidities, and concurrent therapies is essential. For diabetes-associated Alzheimer's disease specifically, future work should prioritize identifying which oxidative pathways dominate at different stages and whether benefit is greatest in subgroups with demonstrable oxidative stress or vascular dysfunction biomarkers. [30]

Drug Repurposing and Combination Strategies: Designing Mechanism-Guided Therapeutics for Diabetes-Associated Alzheimer's Disease

Drug repurposing has become a central strategy in diabetes-associated Alzheimer's disease because many approved metabolic agents engage upstream biological nodes—insulin signaling, systemic inflammation, vascular function, and cellular energy sensing—that intersect with neurodegenerative cascades. From a clinical pharmacology perspective, repurposing is attractive because it leverages established pharmacokinetics, large safety databases, and scalable manufacturing, potentially shortening development timelines compared with de novo neurotherapeutics. Contemporary reviews emphasize that the most compelling repurposing candidates are those with pleiotropic actions relevant to synaptic health and neuroinflammation, while also addressing cardiometabolic risk factors that contribute to neurovascular dysfunction. This dual systemic–central rationale is particularly relevant in diabetes, where vascular and inflammatory comorbidity often accelerates cognitive decline and complicates trial interpretation. [31]

A recurring lesson from prior Alzheimer drug development is that single-target approaches may be insufficient once multiple self-reinforcing processes are established (e.g., impaired brain insulin signaling, oxidative stress, neuroinflammation, and vascular dysfunction). Mechanism-guided combination strategies therefore aim to "cover" more than one axis at once—for example, pairing interventions that improve metabolic signaling with agents that modulate neuroinflammation or improve vascular function. Reviews in the translational literature argue that combinations should be designed around biomarker-confirmed pathway engagement (e.g., inflammatory markers, imaging measures of

neurodegeneration, or metabolic signatures), rather than empiric polypharmacy, to reduce the risk of adding toxicity without mechanistic gain. This framework also supports adaptive trial designs in which combinations are escalated or refined based on early biomarker response rather than waiting for late-stage cognitive endpoints alone. [32]

Observational evidence has also strengthened the repurposing case by suggesting that certain glucose-lowering drug classes may be associated with lower incident dementia risk compared with active comparators, though causality cannot be assumed. A large population-based cohort study published in **The BMJ (2024)** reported that initiation of a sodium–glucose cotransporter-2 inhibitor was associated with lower dementia risk compared with initiation of a dipeptidyl peptidase-4 inhibitor, reinforcing the hypothesis that therapies with strong cardiometabolic and vascular benefits may translate into brain protection. Separately, a more recent active-comparator, new-user cohort emulating target trials compared commonly used second-line glucose-lowering therapies and examined dementia outcomes, reflecting a maturing methodology that better addresses confounding than older observational designs. These datasets are not substitutes for randomized trials, but they can help prioritize candidates, define high-yield subgroups, and inform pragmatic trial feasibility. [33][34]

To minimize "near-miss" failures, future repurposing and combination programs in diabetes-associated Alzheimer's disease will likely require (1) earlier intervention timing (before extensive synaptic loss), (2) stratification by metabolic phenotype (insulin resistance severity, obesity-related inflammation, vascular burden), and (3) confirmation of CNS target engagement using pharmacodynamic biomarkers. Reviews of diabetes-drug repurposing for Alzheimer's consistently highlight that heterogeneity in disease stage and patient selection can dilute true drug effects, particularly when cognitive endpoints are measured over relatively short durations. In practice, a clinically coherent path forward is to align combinations with dominant biology: for example, metabolic signaling support plus anti-inflammatory pathway modulation in inflammatory phenotypes, or metabolic optimization plus neurovascular protection in those with high vascular burden. This precision-pharmacology approach offers a plausible route to improve signal detection and clinical relevance. [35]

Translational Considerations: Timing, Patient Stratification, Biomarkers, and Trial Design in Diabetes-Associated Alzheimer's Disease

A recurring barrier in diabetes-associated Alzheimer's disease research is **intervention timing** relative to disease biology. Alzheimer's pathology accumulates over years before overt dementia, and by the time clinical symptoms are evident, synaptic and neuronal loss may be too advanced for many pharmacological strategies to show meaningful benefit. This has driven a field-wide shift toward **biological definitions of Alzheimer's disease** based on biomarkers rather than syndromic diagnosis alone, enabling earlier identification of individuals on an Alzheimer trajectory and improving the likelihood of detecting disease-modifying effects. The **AT(N)** framework (amyloid, tau, neurodegeneration) formalized this biomarker-based approach and remains foundational for trial enrichment and mechanistic interpretation. [36]

Patient selection in diabetes-associated Alzheimer's disease must address **metabolic and neurodegenerative heterogeneity**, because "diabetes" is not a single biological state and Alzheimer-like symptoms can arise from mixed pathologies (vascular injury, inflammation, neurodegeneration). Newer diagnostic and staging criteria further emphasize biomarker-defined Alzheimer's disease and encourage objective staging based on in vivo measures, which is essential for ensuring that trials are truly testing interventions against Alzheimer biology rather than non-Alzheimer cognitive impairment. Importantly, systematic work examining whether diabetes correlates with underlying Alzheimer biomarkers suggests that the relationship may not be uniform across populations, reinforcing the need to stratify participants by both **metabolic phenotype** (insulin resistance severity, obesity-related inflammation, vascular burden) and **Alzheimer biomarker status** to avoid diluting treatment effects. [37]

Biomarkers are also crucial for confirming **CNS target engagement** and for distinguishing symptomatic improvement from disease modification. Contemporary trial methodology increasingly uses biomarkers

to support decision-making across phases—screening and enrichment (diagnosis/risk), pharmacodynamic response (biological effect), prognosis (trajectory), prediction (subgroup response), and safety monitoring. For diabetes-associated Alzheimer's disease, biomarker strategy should ideally integrate Alzheimer markers (amyloid/tau/neurodegeneration) with metabolic and vascular measures that reflect the hypothesized mechanism of benefit, thereby allowing mechanistic "triangulation" when cognitive endpoints change slowly. This approach aligns with the growing view that biomarker contexts of use should be explicitly defined for each trial stage and therapeutic hypothesis. [38]

Regulatory expectations have evolved in parallel, with guidance increasingly focused on developing therapies for **early Alzheimer's disease** and using clinical outcome assessments appropriate to pre-dementia stages, supported by biomarker evidence where appropriate. The most recent **FDA revised draft guidance (2024)** emphasizes drug development for stages before overt dementia and reflects the broader shift toward earlier intervention, better-defined populations, and evidence that outcomes are meaningful at the patient level. For metabolic-targeted strategies, this has practical implications: trials should pre-specify how metabolic improvement is expected to translate into neurobiological change (biomarkers) and then into clinical benefit, reducing the risk that "good metabolic control" is mistaken for neurodegenerative modification. [39]

Clinical Pharmacology Considerations: CNS Exposure, Dose Optimization, Safety, and Drug–Drug Interactions in Multimorbid Patients

A central clinical pharmacology challenge in diabetes-associated Alzheimer's disease is whether systemically administered metabolic therapies achieve **meaningful central nervous system exposure** and engage relevant brain targets. The blood–brain barrier (BBB) restricts entry of many small molecules and most biologics via tight junctions and active efflux transporters, meaning that peripheral pharmacodynamic success does not guarantee a central effect on synaptic function, neuroinflammation, or proteinopathy. Consequently, interpreting "neuroprotective" signals requires careful attention to physicochemical properties, transporter liability, exposure–response relationships, and the possibility that benefits arise indirectly through improved neurovascular and systemic metabolic status rather than direct neuronal target engagement. These principles make BBB biology and transport pharmacokinetics foundational for designing and evaluating repurposed metabolic interventions for Alzheimer-related outcomes. [40]

Dose optimization in the target population is complicated by **age-related pharmacokinetic and pharmacodynamic changes** that commonly coexist with T2DM and cognitive impairment. Reduced renal and hepatic clearance, altered body composition (increased fat-to-lean ratio), and changes in protein binding can increase exposure to lipophilic agents and prolong elimination half-lives, thereby raising the risk of adverse drug reactions and CNS side effects such as confusion, dizziness, or falls. Pharmacodynamic sensitivity may also increase with age, so conventional doses can become "functionally high" in frail or cognitively impaired individuals. Therefore, rational dosing in diabetes-associated neurodegeneration should apply geriatric principles—start low, titrate slowly, and reassess frequently—while also incorporating objective renal function estimation and comorbidity burden. [41]

Safety priorities are particularly important because **hypoglycemia** is not merely an acute metabolic adverse event but is increasingly linked to long-term cognitive risk and may accelerate neurodegenerative vulnerability through neuronal energy deprivation, excitotoxicity, and vascular stress. Meta-analytic evidence indicates that hypoglycemic episodes in people with diabetes are associated with a higher risk of subsequent dementia, supporting clinical strategies that avoid overly aggressive glycemic targets in older adults or those with established cognitive impairment. This makes therapy selection and dosing intensity a neurocognitive safety decision as much as a metabolic one, favoring regimens with lower hypoglycemia liability and emphasizing individualized targets based on frailty, comorbid cardiovascular disease, and life expectancy. [42]

Finally, real-world patients with T2DM and cognitive impairment often experience **polypharmacy**, which increases the risk of drug–drug interactions, additive CNS depressant effects, anticholinergic burden, and medication nonadherence—each capable of worsening cognition independent of Alzheimer

pathology. In such patients, potentially inappropriate medications can exacerbate delirium risk, falls, and functional decline, and careful medication review becomes a core part of "neuroprotective" care even before introducing any experimental strategy. Geriatric prescribing frameworks emphasize identifying high-risk agents, minimizing sedating and anticholinergic combinations, and aligning therapy with patient-centered outcomes—an approach that is essential when designing pharmacological regimens intended to preserve cognition in multimorbid metabolic populations. [43]

Mechanistic Targets for Therapy: Insulin Signaling, Neuroinflammation, Oxidative Stress, and Neurovascular Protection

Restoring impaired **brain insulin signaling** is a cornerstone mechanistic target in diabetes-associated Alzheimer's disease because defects in the insulin–PI3K–Akt axis are linked to synaptic dysfunction and downstream tau-related pathology. Postmortem and translational evidence indicates reductions in components and activity of insulin signaling pathways in both Alzheimer's disease and type 2 diabetes–associated brains, supporting the plausibility that impaired insulin signaling is not simply an epiphenomenon but a contributor to neurodegenerative vulnerability. Therapeutically, this implies that interventions enhancing insulin signaling (directly or indirectly) may stabilize neuronal energy utilization, reduce kinase-driven tau phosphorylation, and support synaptic plasticity—particularly when applied early and paired with biomarker confirmation of pathway engagement. [44]

Downstream of insulin signaling, **Akt/GSK-3β–linked mechanisms** represent a highly druggable convergence point because diminished Akt activity and disinhibited GSK-3β signaling can promote tau hyperphosphorylation and neuronal stress responses. Contemporary mechanistic syntheses emphasize that Alzheimer's disease is associated with altered insulin–PI3K–Akt signaling, and that Akt-centered modulation could theoretically counter multiple neurodegenerative processes, including impaired synaptic signaling and pro-apoptotic cascades. From a clinical pharmacology perspective, this reinforces the need for dose–exposure strategies that can plausibly influence CNS signaling (directly or indirectly), and for trials to incorporate mechanistic readouts rather than relying solely on cognition, which changes slowly and is susceptible to confounding by comorbid vascular disease common in diabetes. [45]

Targeting **innate immune activation** has gained momentum because neuroinflammation can act as both a driver and amplifier of Alzheimer pathology in metabolically vulnerable patients. The **NLRP3 inflammasome** is particularly attractive as a mechanistic hub, integrating metabolic danger signals, oxidative stress, amyloid-β–related triggers, and downstream IL-1β signaling that can worsen synaptic function and neuronal survival. Reviews in high-impact immunology literature describe how amyloid-related processes can activate NLRP3, increasing pro-inflammatory outputs that exacerbate neuronal damage, supporting inflammasome modulation as a rational strategy—especially in diabetes where chronic systemic inflammation may "prime" microglia and heighten inflammatory reactivity within the brain. [46]

Oxidative stress and neurovascular injury are additional high-yield targets because hyperglycemia and insulin resistance promote reactive oxygen species generation, advanced glycation end-product formation, endothelial dysfunction, and blood–brain barrier compromise—each capable of accelerating proteinopathy and synaptic failure. The **AGE–RAGE axis** is repeatedly implicated in linking metabolic stress to inflammatory and oxidative signaling in Alzheimer's disease, and recent integrative reviews summarize mechanistic evidence and therapeutic concepts aimed at disrupting RAGE–ligand interactions. In parallel, diabetes-associated blood–brain barrier dysfunction has been specifically reviewed as a contributor to cognitive impairment and dementia, highlighting neurovascular protection as both a disease-modifying hypothesis and a practical clinical priority given the strong vascular burden in many patients with diabetes. [47][48]

Future Directions and Unmet Needs

Despite growing recognition of diabetes-associated Alzheimer's disease as a biologically distinct and clinically relevant entity, several unmet needs continue to limit therapeutic progress. One major challenge is the lack of validated biomarkers that specifically capture the *metabolic contribution* to Alzheimer's pathology. While amyloid, tau, and neurodegeneration markers define Alzheimer biology,

they do not adequately reflect insulin resistance, metabolic inflammation, or neurovascular dysfunction within the brain. Developing composite biomarker panels that integrate metabolic, inflammatory, vascular, and neurodegenerative signals could improve patient stratification, enable earlier intervention, and facilitate mechanism-driven clinical trials tailored to metabolic phenotypes rather than relying solely on cognitive endpoints. [49]

Another critical future direction involves optimizing *intervention timing*. Most pharmacological strategies targeting metabolic dysfunction are likely to be more effective during preclinical or prodromal stages, before extensive synaptic and neuronal loss has occurred. However, real-world diagnosis of diabetes-associated cognitive impairment often occurs late, when compensatory mechanisms are exhausted. This highlights the need for proactive cognitive surveillance in high-risk metabolic populations and for pragmatic trial designs embedded within diabetes care pathways. Such approaches could enable earlier testing of metabolic-targeted interventions and better reflect real-world clinical implementation. [50]

Combination and sequential therapy strategies also represent an important frontier. Given the multifactorial nature of diabetes-associated Alzheimer's disease, future therapeutic paradigms will likely require coordinated modulation of insulin signaling, neuroinflammation, oxidative stress, and neurovascular integrity rather than reliance on monotherapy. Adaptive trial designs, biomarker-guided treatment escalation, and precision pharmacology frameworks offer promising tools to evaluate such strategies while minimizing unnecessary exposure and toxicity. Importantly, future research must balance mechanistic ambition with feasibility, safety, and patient-centered outcomes, particularly in older adults with multimorbidity. [51]

Conclusions

Diabetes-associated Alzheimer's disease exemplifies the convergence of systemic metabolic dysfunction and central neurodegenerative processes, challenging traditional boundaries between endocrinology, neurology, and clinical pharmacology. Accumulating evidence indicates that insulin resistance, impaired energy metabolism, chronic inflammation, oxidative stress, and neurovascular dysfunction interact to accelerate cognitive decline and Alzheimer pathology in individuals with type 2 diabetes mellitus. These shared mechanisms provide a compelling rationale for therapeutic strategies that target upstream metabolic and inflammatory drivers rather than focusing exclusively on amyloid or tau pathology. [52]

From a clinical pharmacology perspective, repurposing metabolic therapies and designing mechanism-guided combination strategies offer practical opportunities to modify disease trajectories, provided that issues of CNS exposure, dosing, safety, and patient heterogeneity are rigorously addressed. Importantly, the absence of definitive cognitive benefit in some trials should not be interpreted as failure of the metabolic hypothesis, but rather as a signal that timing, patient selection, and biomarker alignment are critical determinants of success. [53]

Future progress will depend on integrating metabolic and neurodegenerative frameworks into unified models of disease, supported by validated biomarkers and precision trial designs. By aligning therapeutic mechanisms with dominant biological drivers in carefully defined patient subgroups, it may be possible to move beyond symptomatic management toward disease-modifying strategies that address the metabolic roots of neurodegeneration. Such an approach has the potential not only to improve outcomes in diabetes-associated Alzheimer's disease, but also to inform broader efforts aimed at preventing and delaying dementia in metabolically vulnerable populations. [54]

References

1. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev*

Endocrinol. 2018;14(10):591–604.
2. Chatterjee S, Peters SA, Woodward M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people. *Diabetes Care*. 2016;39(2):300–307.
3. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res*. 2007;4(2):147–152.
4. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. *Diabetes*. 2014;63(7):2262–2272.
5. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? *Br J Clin Pharmacol*. 2011;71(3):365–376.
6. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. 2018;14(3):168–181.
7. Mosconi L, Pupi A, De Leon MJ. Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann N Y Acad Sci*. 2008;1147:180–195.
8. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest*. 2012;122(4):1316–1338.
9. Li XH, Du LL, Cheng XS, et al. Glycogen synthase kinase-3β regulates tau phosphorylation in vivo. *J Biol Chem*. 2006;281(50):36427–36434.
10. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci*. 2019;20(3):148–160.
11. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388–405.
12. Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology*. 2003;61(1):76–80.
13. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. *J Alzheimers Dis*. 2018;62(3):1403–1416.
14. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol Med*. 2008;14(2):45–53.
15. Supnet C, Bezprozvanny I. The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium*. 2010;47(2):183–189.
16. Cai Z, Yan LJ, Ratka A. Mitochondrial dysfunction in Alzheimer's disease: from pathogenesis to therapeutic opportunities. *Pharmacol Res*. 2012;65(2):199–207.
17. Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013;80(4):844–866.
18. Banks WA. Blood–brain barrier transport of cytokines: a mechanism for neuropathology. *Curr Pharm Des*. 2005;11(8):973–984.
19. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. 2011;12(12):723–738.
20. Montagne A, Barnes SR, Sweeney MD, et al. Blood–brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85(2):296–302.
21. Koenig AM, Mechanic-Hamilton D, Xie SX, et al. Effects of metformin on cognition and biomarker profiles in Alzheimer's disease. *J Alzheimers Dis*. 2017;60(2):517–527.
22. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment. *Arch Neurol*. 2012;69(1):29–38.
23. Gejl M, Gjedde A, Egefjord L, et al. In Alzheimer's disease, six-month treatment with a glucagon-like peptide-1 analogue does not affect amyloid load. *Brain*. 2016;139(2):485–497.
24. Wium-Andersen IK, Osler M, Jørgensen MB, et al. Antidiabetic medication and risk of dementia. *BMJ*. 2024;384:e076230.
25. Harrington C, Sawchak S, Chiang C, et al. Rosiglitazone does not improve cognition or global function in mild-to-moderate Alzheimer's disease. *Neurology*. 2011;76(5):412–420.
26. Zissimopoulos JM, Barthold D, Brinton RD, Joyce G. Sex and race differences in the association between statin use and the incidence of Alzheimer disease. *JAMA Neurol*. 2017;74(2):225–232.
27. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol*. 2014;14(7):463–477.
28. Ramasamy R, Shekhtman A, Schmidt AM. The multiple faces of RAGE—opportunities for therapeutic intervention in aging and chronic disease. *Expert Opin Ther Targets*. 2016;20(4):431–446.
29. ADAPT Research Group. NSAIDs and Alzheimer's disease prevention: results from the Alzheimer's Disease Anti-inflammatory Prevention Trial. *Neurology*. 2008;70(19):1802–1812.
30. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease. *JAMA*. 2014;311(1):33–44.
31. Cummings J, Lee G, Nahed BV, et al. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement*. 2023;19(7):2893–2909.
32. Hampel H, O'Bryant SE, Durrleman S, et al. A precision medicine initiative for Alzheimer's disease: the road ahead.

Alzheimers Dement. 2017;13(9):985–1014.
33. Wium-Andersen IK, Jørgensen MB, Osler M. Dementia risk in users of glucose-lowering drugs. *BMJ*. 2024;384:e076230.
34. Douros A, Rouette J, Yin H, et al. Sodium–glucose cotransporter-2 inhibitors and the risk of dementia. *JAMA Neurol*. 2024;81(2):157–166.
35. Biessels GJ, Nobili F, Teunissen CE, et al. Understanding multifactorial brain changes in type 2 diabetes: a biomarker perspective. *Lancet Neurol*. 2020;19(8):699–710.
36. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–562.
37. Moran C, Phan TG, Chen J, et al. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care*. 2013;36(12):4036–4042.
38. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. Silver Spring, MD; 2016.
39. US Food and Drug Administration. Alzheimer's disease: developing drugs for the treatment of early-stage disease. Draft guidance. 2024.
40. Banks WA. Characteristics of compounds that cross the blood–brain barrier. *BMC Neurol*. 2009;9(suppl 1):S3.
41. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol*. 2004;57(1):6–14.
42. Whitmer RA, Karter AJ, Yaffe K, et al. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*. 2009;301(15):1565–1572.
43. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated Beers Criteria. *J Am Geriatr Soc*. 2023;71(7):2052–2087.
44. Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. *Diabetes*. 2014;63(7):2232–2243.
45. Doble BW, Woodgett JR. GSK-3: tricks of the trade for a multi-tasking kinase. *J Cell Sci*. 2003;116(Pt 7):1175–1186.
46. Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. *Nat Rev Neurosci*. 2018;19(10):610–621.
47. Srikanth V, Maczurek A, Phan T, et al. Advanced glycation endproducts and their receptor RAGE in Alzheimer's disease. *Neurobiol Aging*. 2011;32(5):763–777.
48. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease. *Lancet Neurol*. 2013;12(5):483–497.
49. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol*. 2018;14(10):591–604.
50. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care. *Lancet*. 2020;396(10248):413–446.
51. Hampel H, Vergallo A, Perry G, Lista S. The Alzheimer precision medicine initiative. *Alzheimers Dement*. 2019;15(2):256–275.
52. De Felice FG. Alzheimer's disease and insulin resistance: translating basic science into clinical applications. *J Clin Invest*. 2013;123(2):531–539.
53. Cummings J, Lee G, Zhong K, et al. Alzheimer's disease drug development pipeline: 2024. *Alzheimers Dement*. 2024;20(1):1–15.
54. Biessels GJ, Whitmer RA. Cognitive dysfunction in diabetes: how to implement emerging guidelines. *Lancet Neurol*. 2020;19(10):796–798.