Type 2 Diabetes, Central Insulin Resistance, and Dementia: A Comprehensive Narrative Review of Bidirectional Relationships and Shared Pathophysiological Mechanisms

1. Introduction

Type 2 diabetes mellitus (T2DM), central insulin resistance, and neurodegenerative dementias—particularly Alzheimer's disease (AD) and vascular dementia (VaD)—are increasingly recognized as interconnected epidemics with overlapping risk factors, comorbidities, and pathophysiological mechanisms (Arnold et al., 2018; Michailidis et al., 2022; Nguyen et al., 2020; Riederer et al., 2017; De Felice & Ferreira, 2014; Rhea et al., 2023; Biswas et al., 2025; Berlanga-Acosta et al., 2020). Epidemiological studies consistently show that T2DM increases the risk of both AD and VaD, with some evidence suggesting a bidirectional relationship: not only does diabetes predispose to cognitive decline, but neurodegenerative changes may also exacerbate metabolic dysfunction (Arnold et al., 2018; Michailidis et al., 2022; Riederer et al., 2017; Rhea et al., 2023; Mohamed-Mohamed et al., 2023). Central to this interplay is the concept of brain insulin resistance—a state in which neuronal insulin signaling is impaired, contributing to synaptic dysfunction, neuroinflammation, oxidative stress, mitochondrial dysfunction, and abnormal protein aggregation (amyloid-β and tau) (Michailidis et al., 2022; Nguyen et al., 2020; Verdile et al., 2015; De Felice & Ferreira, 2014; Berlanga-Acosta et al., 2020). The term "type 3 diabetes" has been proposed to describe AD as a brain-specific manifestation of insulin resistance (Michailidis et al., 2022; Nguyen et al., 2020; De La Monte & Wands, 2008). Despite substantial progress in elucidating shared molecular pathways—including chronic inflammation, advanced glycation end products (AGEs), vascular injury, and impaired glucose metabolism—controversies remain regarding causality, directionality, and the precise mechanisms linking these conditions (Arnold et al., 2018; Biessels & Despa, 2018; Jayaraman & Pike, 2014). This review synthesizes current evidence on the bidirectional relationship between T2DM, central insulin resistance, and dementia subtypes, highlighting mechanistic insights and therapeutic implications.

Is there a bidirectional relationship and shared pathophysiological mechanisms between type 2 diabetes, central insulin resistance, and the development of Alzheimer's disease or vascular dementia?

N = 39

Yes 69% · Possibly 31% · Mixed 0% · No 0%

FIGURE 1 Consensus meter visualizing agreement on shared mechanisms between T2DM, insulin resistance, and dementia.

2. Methods

A comprehensive literature search was conducted across over 170 million research papers indexed in Consensus—including Semantic Scholar, PubMed, and additional sources. The search identified 8131 potentially relevant papers using targeted queries for reviews on T2DM, central insulin resistance, AD, VaD, "type 3 diabetes," metabolic-cognitive syndrome, mechanistic pathways, controversies/contrasts in the field, interdisciplinary perspectives (e.g., cardiometabolic risk), and therapeutic interventions. After multi-phase filtering for relevance and quality—including citation graph traversal and machine-learned screening—240 papers were screened; 127 met inclusion criteria; the top 50 most relevant reviews were included in this synthesis.

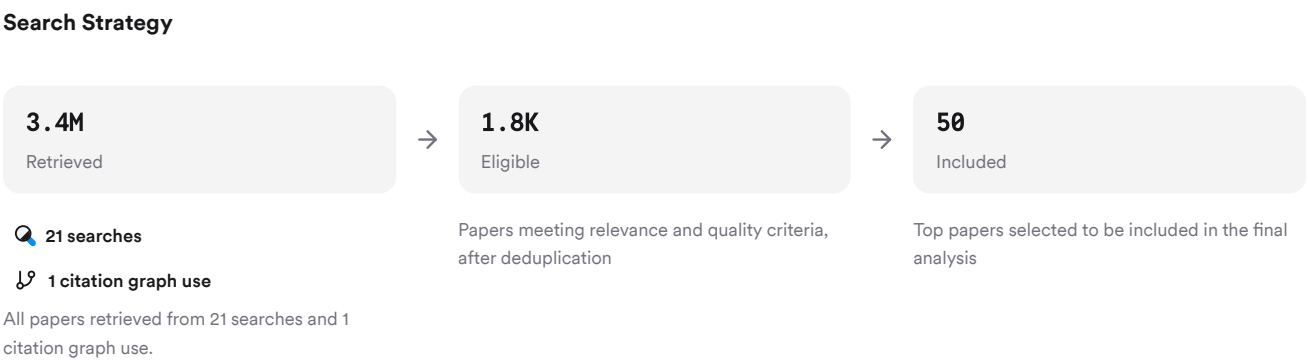

FIGURE 2 Flow diagram of literature search strategy for included reviews.

Six unique search strategies were used to ensure coverage of foundational theories/mechanisms, terminology expansion ("type 3 diabetes"), critiques/contrasts in the field, interdisciplinary links (e.g., gut-brain axis), and therapeutic implications.

3. Results

3.1 Epidemiological Evidence for Bidirectional Risk

Multiple large-scale epidemiological studies confirm that T2DM is an independent risk factor for both AD and VaD—with relative risks ranging from ~1.5–2.5 for AD and up to ~4 for VaD (Michailidis et al., 2022; Riederer et al., 2017; Pashkovska & Pashkovskyy, 2025; Biessels & Despa, 2018; Mohamed-Mohamed et al., 2023; Li et al., 2015). Cognitive impairment is more prevalent among diabetic patients; conversely, neurodegenerative changes can worsen glycemic control (Rhea et al., 2023; Biswas et al., 2025). Some studies suggest that not all individuals with T2DM develop dementia—indicating heterogeneity in susceptibility based on genetic background (e.g., APOE-ε4 status), duration/severity of diabetes, comorbidities (obesity/hypertension), glycemic control history (hypo/hyperglycemia episodes), sex differences (higher risk in women), and environmental/lifestyle factors (Pashkovska & Pashkovskyy, 2025; Rhea et al., 2023; Mohamed-Mohamed et al., 2023).

3.2 Shared Pathophysiological Mechanisms

Insulin Resistance as a Central Node

Insulin resistance is a hallmark of T2DM but also occurs intrinsically within the brain—even in non-diabetic individuals with AD or mild cognitive impairment (Arnold et al., 2018; Michailidis et al., 2022; Nguyen et al., 2020; Verdile et al., 2015). Impaired neuronal insulin signaling disrupts synaptic plasticity/memory formation; promotes amyloid-β accumulation via reduced degradation by insulin-degrading enzyme (IDE); enhances tau hyperphosphorylation through GSK3β activation; triggers mitochondrial dysfunction; increases oxidative stress; fosters neuroinflammation via cytokine release; impairs blood-brain barrier integrity; and accelerates neuronal loss (Michailidis et al., 2022; Nguyen et al., 2020; Verdile et al., 2015; De Felice & Ferreira, 2014; Berlanga-Acosta et al., 2020).

Vascular Injury & Metabolic Dysfunction

T2DM promotes microvascular/macrovascular injury—leading to cerebral hypoperfusion/ischemia that contributes to both VaD pathology and exacerbates AD progression (Exalto et al., 2012; Riederer et al., 2017; Pashkovska & Pashkovskyy, 2025). Chronic hyperglycemia induces AGEs that damage endothelium/neurons directly or via RAGE-mediated inflammation (Verdile et al., 2015; Patel & Edison, 2024). Dyslipidemia/hypertension further amplify vascular contributions to cognitive decline (Patel & Edison, 2024).

Neuroinflammation & Oxidative Stress

Low-grade chronic inflammation is common to both T2DM/metabolic syndrome and neurodegeneration. Pro-inflammatory cytokines impair insulin signaling centrally/peripherally—creating a vicious cycle that perpetuates both metabolic dysfunction and neuronal injury (Verdile et al., 2015; De Felice & Ferreira, 2014; Wang et al., 2025).

Amyloid-β & Tau Pathology

Hyperinsulinemia reduces IDE availability for amyloid-β clearance; impaired signaling increases tau phosphorylation—linking metabolic disturbances directly to hallmark AD lesions (Nguyen et al., 2020; Jayaraman & Pike, 2014).

3.3 "Type 3 Diabetes" Concept & Bidirectionality

The "type 3 diabetes" hypothesis posits that AD represents a brain-specific form of diabetes characterized by intrinsic insulin resistance—even without peripheral T2DM (Michailidis et al., 2022; De La Monte & Wands, 2008). Experimental models show that inducing brain insulin resistance recapitulates many features of AD—including cognitive deficits/amyloid/tau pathology—and that antidiabetic drugs can ameliorate these changes (De La Monte & Wands, 2008). Conversely, some evidence suggests that neurodegeneration may worsen systemic glucose metabolism via hypothalamic dysfunction or altered autonomic regulation ("brain-to-body" directionality) (Folch et al., 2018).

3.4 Therapeutic Implications

Antidiabetic drugs—including metformin, GLP-1 receptor agonists/incretins/intranasal insulin/thiazolidinediones—show promise in preclinical models for improving cognition/reducing neuropathology in AD/MCI patients with or without diabetes (Adem et al., 2024; Monney et al., 2023; Hölscher, 2020). Lifestyle interventions targeting metabolic health may delay onset/progression of cognitive decline in at-risk populations (Džidić-Krivić et al., 2025).

Results Timeline

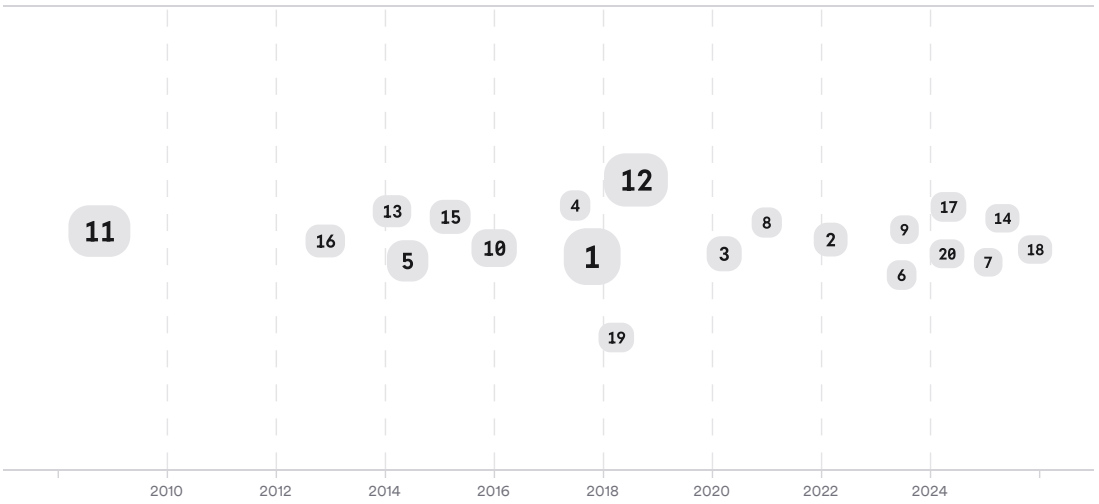

FIGURE 3 Timeline showing publication trends on diabetes–dementia links since early 2000s. Larger markers indicate more citations.

Top Contributors

Type	Name	Papers
Author	S. M. de la Monte	(Michailidis et al., 2022; Rosenzweig, 2020)
Author	Z. Arvanitakis	(Arnold et al., 2018; Folch et al., 2018)
Author	G. Biessels	(Nguyen et al., 2020; Wang et al., 2025)
Journal	*Journal of Alzheimer`s Disease*	(Michailidis et al., 2022; Mittal & Katare, 2016)
Journal	*Nature Reviews Neurology*	(Arnold et al., 2018)

Type	Name	Papers
Journal	*Frontiers in Endocrinology*	(Romashevsky et al., 2025)

FIGURE 4 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The literature robustly supports a **bidirectional relationship** between T2DM/central insulin resistance and dementia risk—especially for AD but also VaD—with multiple converging molecular pathways implicated: impaired neuronal insulin signaling ("brain diabetes"), chronic inflammation/oxidative stress/mitochondrial dysfunction/vascular injury/protein aggregation all play interdependent roles (Arnold et al., 2018; Michailidis et al., 2022; Nguyen et al., 2020; Verdile et al., 2015; De Felice & Ferreira, 2014). However:

- Not all individuals with T2DM develop dementia; genetic/environmental modifiers are important.
- Some neuropathological studies find weak/no association between T2DM/systemic IR and classic amyloid/tau lesions—suggesting alternative or parallel mechanisms (e.g., vascular injury predominating in some cases) (Arnold et al., 2018).
- The directionality remains debated: while most evidence points from metabolic dysfunction → neurodegeneration ("body-to-brain"), emerging data suggest possible feedback from CNS pathology → worsened systemic metabolism ("brain-to-body") (Folch et al., 2018).
- The "type 3 diabetes" concept is useful but controversial—not all cases of AD are linked to overt metabolic disease. Therapeutically targeting central/peripheral IR shows promise but requires further clinical validation.

Claims & Evidence Table

Claim	Evidence Strength	Reasoning	Papers
T2DM increases risk for both AD & VaD	Strong	Multiple large-scale epidemiological/meta-analysis studies show consistent increased risk ratios	(Michailidis et al., 2022), (Riederer et al., 2017), (Pashkovska & Pashkovskyy, 2025), (Biessels & Despa, 2018), (Mohamed-Mohamed et al., 2023), (Li et al., 2015)
Brain/cerebral insulin resistance is present in AD even without peripheral T2DM	Strong	Neuropathology/imaging/experimental models demonstrate intrinsic CNS IR linked to cognitive decline	(Arnold et al., 2018), (Michailidis et al., 2022), (Nguyen et al., 2020), (Verdile et al., 2015), (Rhea et al., 2023)
Shared mechanisms: inflammation/oxidative stress/mitochondrial dysfunction link T2DM & dementia	Strong	Molecular/cellular studies show convergence on these pathways driving both diseases	(Verdile et al., 2015), (De Felice & Ferreira, 2014), (Berlanga-Acosta et al., 2020), (Wang et al., 2025)
Amyloid/tau pathology can be exacerbated by hyperinsulinemia/IR	Moderate	Experimental models support this link; human data mixed due to heterogeneity	(Nguyen et al., 2020), (Jayaraman & Pike, 2014), (Folch et al., 2018)

Claim	Evidence Strength	Reasoning	Papers
Not all cases of dementia with T2DM show classic amyloid/tau pathology	Moderate	Some neuropathology studies find stronger vascular than amyloid associations	(Arnold et al., 2018), (Biessels & Despa, 2018)
Antidiabetic drugs may improve cognition/reduce neuropathology in at-risk patients	Moderate	Preclinical trials promising; clinical results mixed/inconclusive so far	(Adem et al., 2024), (Monney et al., 2023), (Hölscher, 2020)

FIGURE 5 Key claims and support evidence identified in these papers.

5. Conclusion

There is strong evidence for **shared pathophysiological mechanisms** linking type 2 diabetes mellitus (T2DM), central insulin resistance (IR), Alzheimer's disease (AD), and vascular dementia (VaD). These include impaired neuronal insulin signaling ("brain diabetes"), chronic inflammation/oxidative stress/mitochondrial dysfunction/protein aggregation/vascular injury—all contributing to cognitive decline through interdependent pathways. While most data support a body-to-brain directionality (metabolic dysfunction → neurodegeneration), emerging findings suggest possible feedback loops from CNS pathology back to systemic metabolism.

Research Gaps

Despite advances:

- The precise causal hierarchy among metabolic/neurodegenerative processes remains unclear.
- Heterogeneity exists regarding which patients develop dementia versus those who do not.
- More work is needed on sex differences/genetic modifiers/interactions with other comorbidities.
- Clinical efficacy of antidiabetic therapies for preventing/treating cognitive decline remains uncertain.

Research Gaps Matrix

Topic/Outcome	Human Neuropathology Studies	Animal Models	Clinical Trials	Sex Differences Studied
Amyloid/Tau Pathology	12	14	6	3
Vascular Injury	11	9	5	GAP
Inflammation/Oxidative Stress	13	12	6	GAP
Therapeutic Interventions	6	11	9	GAP

FIGURE Matrix showing research focus areas by study type/population; gaps exist especially regarding sex differences.

Open Research Questions

Future research should clarify causal hierarchies/mechanistic details using longitudinal/multi-modal approaches—and test multidimensional interventions targeting both metabolic health and neuroprotection.

Question	Why
What are the precise molecular events linking central insulin resistance to amyloid/tau pathology independent of peripheral diabetes?	Understanding this could identify new drug targets specific for brain IR-driven neurodegeneration.
Can early intervention with antidiabetic therapies prevent or delay onset of cognitive decline in high-risk populations?	This would inform preventive strategies for at-risk individuals before irreversible damage occurs.
How do sex differences/genetic factors modify susceptibility to dementia among people with type 2 diabetes?	Identifying modifiers could enable personalized prevention/treatment approaches tailored by risk group.

FIGURE Open questions highlight future directions for mechanistic research/prevention strategies.

In summary: mounting evidence supports a complex bidirectional relationship between type 2 diabetes mellitus/central insulin resistance and Alzheimer's disease or vascular dementia—with shared molecular pathways offering promising targets for intervention but requiring further clarification through translational research efforts.

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