Review

Exploring the link between GLP-1 receptor agonists and dementia: A comprehensive review

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Abstract

Type 2 diabetes mellitus (T2DM) and insulin resistance are associated with an increased risk of cognitive decline and dementia, including Alzheimer's disease (AD). Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for glycemic control, are emerging as neuroprotective agents. This review evaluates the evidence regarding the effects of GLP-1RAs in populations with T2DM-both with and without cognitive impairment, as well as in individuals diagnosed with AD. We conducted a comprehensive literature search and identified ten studies for inclusion: six randomized controlled trials, one prospective open-label study, and three observational studies. GLP-1RAs consistently demonstrated cognitive benefits in patients with T2DM, even in the absence of metabolic improvements. In cases of early dementia or AD, GLP-1RA treatment preserved brain metabolism and connectivity but did not significantly alter amyloid or tau biomarkers. Notably, cognitive improvements were most evident in individuals with higher body mass index (BMI) or obesity. While some studies reported neural functional changes via imaging, direct modifications in established AD biomarkers were not consistently observed. In conclusion, GLP-1RAs may improve cognitive outcomes and brain function, particularly in the early stages of neurodegeneration and among high-risk T2DM populations. Further well-designed clinical trials are needed to evaluate the impacts of GLP-1RAs on both the clinical progression and underlying pathology of dementia.

Keywords

Alzheimer's disease, cognition, dementia, GLP-1RA

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Introduction

Type 2 diabetes and insulin resistance have been increasingly linked to the development of cognitive decline and dementia, including Alzheimer's disease (AD). Insulin resistance-both systemic and cerebral-impairs insulin signaling, which is essential for neuronal function, memory formation, and synaptic plasticity. Research has shown that individuals with diabetes and insulin resistance are at significantly higher risk of developing dementia, due to the interplay of metabolic dysfunction, oxidative stress, inflammation, and neurodegeneration. This connection has spurred the exploration of therapeutic strategies aimed at improving insulin sensitivity to mitigate the risk of dementia.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were originally developed to treat type 2 diabetes (T2DM) by stimulating insulin secretion from pancreatic beta

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cells under hyperglycemic conditions and reducing glucagon secretion from alpha cells, thereby restoring insulin sensitivity and improving glycemic homeostasis.[1,2]

GLP-1RAs have been found to possess anti-inflammatory and antioxidant properties, which help reduce inflammation and oxidative stress in the brain—factors known to contribute to neurodegenerative diseases such as AD.[3] In addition to these effects, GLP-1RAs improve brain insulin sensitivity. Since insulin resistance in key brain regions such as the hippocampus is associated with cognitive decline, the ability of GLP-1RAs to cross the blood-brain barrier and enhance insulin signaling may help preserve neuronal function.[4,5] Furthermore, these analogues promote neuronal survival and support synaptic plasticity-critical processes for memory and learning-potentially helping to slow cognitive decline.[6] Recent studies also suggest that GLP-1RAs can reduce amyloid-β (Aβ) deposition and tau hyperphosphorylation, hallmark pathologies of AD, reinforcing their potential role in preventing or mitigating dementia.[7]

Given the emerging evidence, this review aims to evaluate the findings from clinical studies that examine the relationship between GLP-1RAs and dementia, offering insights into their potential role in cognitive preservation and the treatment of neurodegenerative diseases.

Objectives

The objective of this study was to assess the association between GLP-1RA and dementia.

Methods

Search strategy

We conducted a comprehensive literature search using the PubMed database, covering the period from January 1, 2014, to July 15, 2024. The search was restricted to studies published in English. Our search strategy combined the terms 'dementia' and 'GLP-1.' Additionally, a manual search of the reference lists from selected articles was performed to identify further relevant studies.

Eligibility criteria and study selection

Studies were included if they reported an association between GLP-1RAs and dementia. Animal and in vitro studies were excluded.

The search yielded 277 titles and abstracts from PubMed, of which 13 articles were retrieved for full-text review. Five articles were excluded due to irrelevance to the topic. Additionally, two studies were identified through a manual search of references cited in the selected articles. Ultimately, ten studies met the inclusion criteria, comprising six randomized controlled trials (RCTs), one prospective open-label, and three observational studies. Of these, six examined cognitive function, five focused on imaging, one investigated biomarker, and three reported on incidence. All studies included in our review are summarized in Table 1.

Results

Cognitive function

Studies on the cognitive impact of GLP-1RAs show diverse outcomes, with significant differences often influenced by study design, patient demographics, and the stage of dementia. Observational studies in populations with T2DM and prediabetes have provided the strongest evidence for cognitive improvements. For example, Li et al. (2021)[16] observed that patients with T2DM treated with liraglutide showed significant improvements in total learning ($p = 0.039$), naming test ($p = 0.025$) and Mini-Mental State Examination (MMSE) score ($p = 0.001$), independent of metabolic improvements. Similarly, Vadini et al. (2020)[13] reported enhanced short-term memory (delta Digit Span Z score: −0.06 to 0.80, $p = 0.024$) and memory composite z-score (mean memory z-score: −0.67 to 0.032, $p = 0.0065$) in obese patients with prediabetes or early-stage T2DM who received liraglutide treatment. These findings suggest that cognitive benefits may be more pronounced in individuals with metabolic risk factors and early cognitive decline.

In contrast, RCTs like those conducted by Watson et al. (2019)[10] and Gejl et al. (2016)[8] observed only modest improvements in people living with AD, primarily in specific cognitive domains such as orientation, without significant enhancements in global cognition. Mullins et al. (2019)[11] reported improvement in attention (Digit Span Forward total score, $p = 0.006$) in patients treated with exenatide, though no significant effects were observed in other cognitive domains, highlighting potential limitations of GLP-1RAs in advanced stages of dementia.

Overall, the strongest cognitive benefits were observed with early interventions in individuals with prediabetic or early-stage T2DM, suggesting a potential role for GLP-1RAs in slowing cognitive decline when introduced at earlier stages of neurodegeneration.

Evidence from observational studies

Observational studies and non-randomized trials provide supportive evidence for the neuroprotective potential of GLP-1RAs, particularly in metabolically at-risk populations vulnerable to cognitive decline. In a prospective open-label study, Li et al. (2021)[16] reported that patients with T2DM treated with liraglutide showed improvements in MMSE scores ($p = 0.001$), which were maintained independently of weight loss or glycemic control-suggesting a direct neuroprotective effect rather than a metabolic-mediated one. In a nested case-control study, Wium-Andersen et al. (2019)[12] found that antidiabetic drugs, particularly GLP-1RAs, were associated with a lower risk of developing dementia (OR

Table 1. Summary of clinical studies examining the association between GLP-1RA and dementia.

Study, year	Study design	Study population	Intervention	Duration	Key findings	Type of results
Gejl, 2016[8]	RCT	38 subjects 50–80 years, Caucasians AD patients without diabetes	liraglutide or placebo	26 weeks	Liraglutide treatment prevented the expected decline of glucose metabolism (CMRglc) that reflects disease progression. No differences between the groups treated with liraglutide and placebo with respect to amyloid deposition or cognition.	Cognition – WMS-IV Imaging - [^{11}C]PIB (PIB), CMR_{glc} with [^{18}F] FDG(FDG) Others – N/A
Gejl, 2017[9]	RCT	38 subjects, 50–80 years, Caucasians AD patients without diabetes	liraglutide or placebo	26 weeks	Liraglutide treatment highly significantly raised the T_{max} estimates of cerebral cortex from 0.72 to 1.1 µmol/g/min, equal to T_{max} estimates in healthy volunteers.	Cognition – N/A Imaging – blood brain glucose transfer capacity (T_{max}) Others – N/A
Watson, 2019[10]	RCT	43 subjects, 45–70 years with subjective cognitive complaints and a MMSE score of > 27, exclude subjects with overt DM	liraglutide or placebo	12 weeks	There were no detectable cognitive differences between study groups after 12 weeks treatment. Increase brain connectivity in the default mode network among individuals randomized to the liraglutide group.	Cognition – BVRT, CVLT-II, D-KEFS, RCFT, Purdue Pegboard, WAIS-III, WASI Imaging - fMRI
Mullins, 2019[11]	RCT	27 subjects >60 years MCI or mild AD patients without diabetes	exenatide or placebo	18 months	Exenatide treatment produced no differences or trends compared to placebo for clinical and cognitive measures, MRI cortical thickness and volume, or biomarkers in CSF, plasma, and plasma neuronal EV except for a reduction of Aβ42 in EVs. Exenatide group has significant for Digit-Span forward total score ($p = 0.006$) and maximum digit span forward ($p = 0.017$).	Cognition – MMSE, ADAS-Cog, FAB, CVLT, Verbal Fluency, Boston Naming Test, TMT, ANART, Clock drawing, BVRT, UPSIT Imaging - MRI cortical thickness and volume Others - biomarkers in CSF, plasma, and plasma neuronal extracellular vesicles
Wium-Andersen, 2019[12]	Nested case control cohort Study	176,250 patients registered with type 2 diabetes in the Danish	Antidiabetic medication (insulin, metformin, sulfonylurea and glinides	N/A	Use of metformin, DPP4 inhibitors, GLP-1RA, and SGLT2 inhibitors were	Cognition – N/A Imaging – N/A Others - incidence

(continued)

Table 1. Continued.

Study, year	Study design	Study population	Intervention	Duration	Key findings	Type of results
		National Diabetes Register between 1995 and 2012	combined, glitazone, DPP4 inhibitor, GLP-1RA, SGLT2 inhibitors and acarbose)		associated with lower odds of dementia after multiple adjustments (ORs of 0.94 [95% CI: 0.89–0.99], 0.80 [95% CI: 0.74–0.88], 0.58 [95% CI: 0.50–0.67], and 0.58 [95% CI: 0.42–0.81], respectively), with a gradual decrease in odds of dementia for each increase in daily defined dose	(dementia diagnosis by ICD-10 or prescriptions of anti-dementia medication until May 2018)
Vadini, 2020[13]	RCT	40 subjects with pre-diabetes or early T2DM, BMI > 30	Liraglutide or lifestyle counseling until achieving 7% weight loss of initial body weight	N/A	A significant increase in short term memory (mean Digit Span Z score from −0.06 to 0.80, $p = 0.024$) and memory composite z-score (mean memory z-score from −0.67 to 0.032, $p = 0.0065$) was observed in the liraglutide exposed subjects (between group $p = 0.041$ and $p = 0.033$, respectively).	Cognition –memory, attention, and executive Imaging – N/A Others – N/A
Akimoto, 2020[14]	Retrospective cohort	66,085 patients, ≥ 65 years with monotherapy T2DM	different antidiabetic drug monotherapies compared to that of metformin monotherapy	N/A	Rosiglitazone ([aROR] 0.11; 95% CI: 0.07–0.17; $p < 0.001$), exenatide (aROR 0.22; 95% CI: 0.11–0.37; $p < 0.001$), liraglutide (aROR 0.36; 95% CI: 0.19–0.62; $p < 0.001$), dulaglutide (aROR 0.39; 95% CI: 0.17–0.77; $p < 0.014$), and sitagliptin (aROR 0.75; 95% CI: 0.60–0.93; $p < 0.011$) were found to have a significantly lower associated risk of AD than that of metformin.	Cognition – N/A Imaging – N/A Others – Incidence (prescriptions of anti-dementia medication)
Cukierman-Yaffe, 2020[15]	Secondary analysis of RCT	9901 participants, aged ≥ 50 years 371 sites in 24 countries	Dulaglutide or placebo	Median follow-up was 5.4 (IQR 5.1–5.9) years	Hazard of substantive cognitive impairment was reduced by 14% in dulaglutide group (HR 0.86, 95% CI 0.79–0.95; $p = 0.0018$)	Cognition – MoCA, DSST Imaging – N/A Others – N/A

(continued)

Table 1. Continued.

Study, year	Study design	Study population	Intervention	Duration	Key findings	Type of results
Li, 2021[16]	Prospective, parallel assignment, open-label, phase III study	50 subjects with T2DM, age 18 to 65 years	liraglutide or control group (oral antidiabetic drugs or combined with insulin)	12 weeks	Patients in liraglutide group acquired better scores in cognitive tests and showed improvement in memory and attention ($p = 0.040$) test compared with the control group. Compared with the control group, liraglutide significantly increased activation of the dorsolateral prefrontal cortex and orbitofrontal cortex brain regions ($p = 0.0038$). After liraglutide treatment, cognitive scores were significantly correlated with changes in these activating brain regions ($p < 0.05$).	Cognition – memory, execution, and verbal Imaging - fNIRS Others – N/A
Tang, 2024[17]	Observational emulated trial study	88,381 subjects with T2DM, age 65 years or older	GLP-1RA, DPP-4i, or sulfonylureas	Average 4.3 years	GLP-1RA was associated with a reduced risk of dementia compared to sulfonylureas (HR 0.69) and DPP-4i (HR 0.77)	Others – Incidence (ICD-10)

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive; ANART: American National Adult Reading Test; aROR: adjusted reporting odds ratio; Aβ: amyloid-β; BMI: body mass index; BVRT: Benton Visual Retention Test; CI: confidence interval; CMRglc: cerebral metabolic rate of glucose; CSF: cerebrospinal fluid; CVLT: California Verbal Learning Test; D-KEFS: Delis-Kaplan Executive Function System; DM: diabetes mellitus; DPP4: dipeptidyl peptidase 4; DPP-4i: dipeptidyl peptidase 4 inhibitor; DSST: Digit Symbol Substitution Test; EV: extracellular vesicles; FAB: Frontal Assessment Battery; fMRI: functional magnetic resonance imaging; fNIRS: functional near-infrared spectroscopy; GLP-1RA; glucagon-like peptide-1 receptor agonist; HR: hazards ratio; ICD-10: International Classification of Diseases, 10th version; IQR: interquartile range; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; N/A: not applicable; ORs: odds ratio; RCFT: Rey Complex Figure Test and Recognition Trial; RCT: randomized controlled trial; SGLT2: sodium-glucose transport protein 2; T2DM: type 2 diabetes mellitus; TMT: Trail Making Test; UPSIT: University of Pennsylvania Smell Identification Test; WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition; WASI: Wechsler Abbreviated Scale of Intelligence; WMS-IV: Wechsler Memory Scale, 4th edition.

0.80, 95% CI 0.74–0.88), although the study did not directly assess cognitive function improvements. Additionally, Akimoto et al. (2020)[14] analyzed data from the FDA Adverse Event Reporting System (FAERS) and found a reduced risk of AD in patients with T2DM using GLP-1RAs: exenatide (aROR 0.22, 95% CI 0.11–0.37, $p < 0.001$), liraglutide (aROR 0.36, 95% CI 0.19–0.62, $p < 0.001$), and dulaglutide (aROR 0.39, 95% CI 0.17–0.77, $p < 0.014$), indirectly supporting their potential role in cognitive preservation. Adding to this evidence, Tang et al. (2024)[17] conducted an emulated target trial using Swedish national registry data and found that initiation of GLP-1RA therapy was associated with a significantly reduced risk of dementia compared to sulfonylureas (HR 0.69, 95% CI 0.60–0.79) and DPP-4 inhibitors (HR 0.77, 95% CI 0.68–0.88), with findings robust across sensitivity analyses.

Evidence from randomized controlled trials (RCTs)

RCTs provide more controlled evidence of the cognitive effects of GLP-1RAs, though the results are mixed. For instance, Watson et al. (2019)[1] did not observe cognitive improvements among patients with subjective cognitive decline, suggesting limited benefit in individuals without objective deficits. The REWIND trial, originally designed to assess cardiovascular outcomes in individuals with T2DM and additional cardiovascular risk factors, included a secondary exploratory analysis by Cukierman-Yaffe et al. (2020)[15] to evaluate cognitive outcomes. This analysis found that dulaglutide modestly slowed cognitive decline over time (HR 0.93, 95%CI 0.85–1.02, $p = 0.11$), with more pronounced effects among participants with lower baseline cognitive scores ($p_{interaction} = 0.0043$ for MoCA). However, the overall impact on global cognition was small and must be interpreted in the context of the trial's original cardiovascular focus.

Gejl et al. (2016)[8] reported that liraglutide preserved orientation in people living with AD, but did not significantly improve other cognitive domains ($p = 0.99$). Similarly, Mullins et al. (2019)[11] found that exenatide treatment led to improved attention scores, although global cognitive function remained unchanged. Vadini et al. (2020)[13] showed that liraglutide significantly enhanced short-term memory in obese patients with prediabetes (delta Digit Span Z score: −0.06 to 0.80, $p = 0.024$), supporting its potential benefit as an early cognitive intervention. Collectively, these findings suggest that GLP-1RA-associated cognitive benefits are most evident during early stages of cognitive decline, rather than in advanced dementia.

Aβ and other biomarkers

Few studies have assessed the effects of GLP-1RAs on AD biomarkers, particularly Aβ accumulation. Gejl et al. (2016)[8] used [^{11}C]PIB PET scans to measure Aβ levels and found no significant changes ($p \geq 0.38$) following liraglutide treatment, suggesting that GLP-1RAs may not affect amyloid plaque deposition in the short-term. Similarly, Mullins et al. (2019)[11] found no significant treatment effects on biomarkers in cerebrospinal fluid, plasma, or plasma neuronal extracellular vesicles (EVs), with only a minor change in $A\beta_{42}$ levels in EVs after exenatide treatment ($p = 0.045$). In contrast, Akimoto et al. (2020)[14] reported improvements in insulin signaling markers, particularly phosphorylated IRS-1, which may enhance brain insulin sensitivity and provide indirect neuroprotective effects. These findings suggest that while GLP-1RAs may not directly influence amyloid pathology, they could support brain health via alternative mechanisms.

Cerebral glucose metabolism

GLP-1RAs show promise in preserving cerebral glucose metabolism, which is frequently compromised in AD. Gejl et al. (2016)[8] demonstrated that liraglutide treatment prevented the typical decline in the cerebral metabolic rate of glucose (CMRglc), particularly in the precuneus, parietal, and occipital lobes—regions critically involved in cognition. While the placebo group experienced significant declines in glucose metabolism ($p = 0.04$), liraglutide-treated participants exhibited slight numerical increase, suggesting that GLP-1RAs may help maintain energy metabolism and cognitive function, especially in the early stages of AD.

Brain signaling and atrophy

Functional MRI studies provide evidence of GLP-1RAs enhance connectivity between brain regions responsible for memory and executive function. Watson et al. (2019)[10] reported that liraglutide improved connectivity within the default mode network, a network essential for memory processing and commonly disrupted in AD. Similarly, Li et al. (2021)[16] observed enhanced connectivity between the hippocampus, insula, and medial frontal cortex in patients receiving liraglutide. Gejl et al. (2016)[8] also founded improvements in connectivity in people living with AD, although the effects were less prominent in advanced stages. However, MRI studies on structural brain changes, such as cortical thickness or volume, have shown no significant effects following short-term GLP-1RA treatment. Mullins et al. (2019)[11] found no reduction in cortical atrophy after exenatide treatment. These findings suggest that while functional connectivity may improve, structural preservation may require longer treatment durations.

Metabolic measures

GLP-1RAs consistently improve metabolic parameters such as glycemic control and weight loss in patients with T2DM.

Li et al. (2021)[16] and Vadini et al. (2020)[13] both reported reduction in HbA1C and body weight following liraglutide treatment among patients with diabetes and prediabetes. Notably, these studies also found that cognitive improvements occurred independently of metabolic changes, suggesting that GLP-1RAs may exert direct neuroprotective effects beyond metabolic regulation. Watson et al. (2019)[10] observed slight metabolic improvements with liraglutide ($p = 0.06$), though these changes were not directly associated with cognitive benefits. This implies that GLP-1RAs may influence brain function through pathways distinct from their metabolic effects.

Discussion

Dementia is a chronic condition characterized by progressive cognitive decline, diminished quality of life, and loss of independence. Diabetes represents a major risk factor for dementia, likely through intertwined metabolic and vascular mechanisms. Recent studies suggest that GLP-1RAs may exert neuroprotective effects, providing cognitive benefits, biomarker modulation, and improvements in overall brain function.

Cognitive outcomes associated with GLP-1RA use are mixed and appear to depend on baseline cognitive and health status. Li et al. (2021)[16] and Vadini et al. (2020)[13] demonstrated improvements in memory and attention, particularly in individuals with higher BMI and mild cognitive impairment. These findings underscore the importance of early intervention and align with preclinical data showing neuroprotective effects of GLP-1RAs in early AD models. Conversely, Gejl et al. (2016)[8] reported limited efficacy in advanced AD, possibly reflecting decreased neuronal plasticity at later stages. These differences suggest that a targeted therapeutic approach may be most effective, with GLP-1RAs offering the greatest benefit in early dementia or mild cognitive impairment.

Evidence on the impact of GLP-1RAs on AD's biomarkers, particularly amyloid-beta, remains limited. Neither Gejl et al. (2016)[8] nor Mullins et al. (2019)[11] observed significant changes in amyloid-beta levels following treatment, suggesting limited effects on amyloid pathology within current study durations. Although GLP-1RAs may exerts benefit through alternative pathways such as reduced neuroinflammation or synaptic protection, longer trials with comprehensive biomarker analyses are needed to determine any potential effects on amyloid or tau proteins.

GLP-1RAs appear promising in preserving cerebral glucose metabolism, a critical factor in AD pathology. Gejl et al. (2016)[8] showed that liraglutide helped sustain metabolic activity in brain regions commonly affected in AD. Functional MRI findings from Watson et al. (2019)[10] and Li et al. (2021)[16] support this, showing enhanced connectivity in memory and executive function networks, potentially delaying neurodegeneration.

This review's strength lies in its comprehensive analysis of both RCTs and observational studies, offering insights into the potential of GLP-1RAs across varied populations. However, limitations include small sample sizes, short follow-up periods, and heterogeneous methodologies. While observational data provide valuable real-world evidence, they often lack standardized cognitive assessments, which may limit generalizability. Nonetheless, Tang et al. (2024)[17] provided compelling evidence from a nationwide emulated trial, showing that GLP-1RA use was significantly associated with reduced dementia risk compared to DPP-4 inhibitors and sulfonylureas.

Conclusion

GLP-1RAs show promise in improving cognitive outcomes in early-stage dementia, particularly among patients with higher BMI and mild cognitive impairment. Their effects may extend beyond metabolic improvements, potentially preserving cerebral glucose metabolism and enhancing brain connectivity. A precision medicine approach-considering baseline cognitive and metabolic status-may help optimize therapeutic benefits. Further long-term studies are needed to clarify the role of GLP-1RAs in modifying AD pathology and supporting brain health.

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Data availability statement

No datasets were generated or analyzed during the current study.

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