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THE ROLE OF INCRETIN-BASED THERAPIES IN ALZHEIMER'S DISEASE: FOCUS ON SEMAGLUTIDE - LITERATURE REVIEW

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ABSTRACT

Background: Alzheimer's disease is increasingly recognized as a disorder with metabolic and inflammatory components linked to insulin resistance and impaired glucose metabolism. Incretin-based therapies, particularly GLP-1 receptor agonists, have emerged as potential disease-modifying candidates due to their neuroprotective and metabolic actions.

Aims: To provide a comprehensive and critical synthesis of current evidence on incretin-based therapies with a focus on semaglutide in Alzheimer's disease, integrating mechanistic, preclinical, and clinical findings, and to identify key research gaps and priorities for future studies.

Methods: A narrative evidence-based review was conducted in accordance with PRISMA principles. Literature was searched in PubMed and Google Scholar for English-language publications from February 2023 to June 2025 using the keywords "Alzheimer's disease," "semaglutide," and "GLP-1 receptor agonists." A total of 439 records were identified; 40 publications were analyzed, and 16 studies met the inclusion criteria for qualitative synthesis (7 preclinical, 5 clinical, and 4 reviews).

Results: In preclinical models, semaglutide improved cognition, reduced neuroinflammation and oxidative stress, and attenuated β-amyloid and tau pathology. Early clinical and observational studies indicate potential neuroprotective effects and an acceptable safety profile, although data remain heterogeneous and underpowered. Evidence concerning blood–brain barrier (BBB) penetration, dose - response dynamics, and comparative efficacy versus other GLP-1RAs is still incomplete.

Conclusions: Semaglutide represents a biologically plausible and clinically promising candidate for disease modification in Alzheimer's disease. Confirmation requires long-term, placebo-controlled clinical trials with standardized cognitive and biomarker endpoints, predefined patient stratification by metabolic status and APOE4 genotype, exploration of alternative administration routes, and identification of predictors of therapeutic response.

Keywords: Alzheimer's disease; semaglutide; GLP-1 receptor agonists; neuroprotection; insulin resistance; cognition; disease modification

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and remains one of the greatest challenges for global public health. It accounts for nearly two-thirds of all dementia cases worldwide, and the number of affected individuals is projected to exceed 150 million by 2050 [1].

AD is a progressive neurodegenerative disorder leading to memory loss, cognitive decline, behavioral alterations, and functional dependence. Although aging is the main risk factor, the disease develops through a multifactorial mechanism that involves genetic predispositions (especially the APOE4 allele), vascular dysfunction, and metabolic disorders such as type 2 diabetes mellitus (T2DM). The high prevalence of insulin resistance and impaired glucose utilization in the brains of AD patients has led to the concept of "type 3 diabetes," highlighting a metabolic dimension in neurodegenerative pathology [2].

This concept has shifted the research focus toward therapeutic strategies capable of modifying both metabolic and neuroinflammatory pathways. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for T2DM and obesity, have shown pleiotropic actions on the central nervous system, including improved insulin signaling, mitochondrial protection, and suppression of oxidative and inflammatory damage [3].

Among this class, semaglutide possesses distinct pharmacological advantages. Its prolonged half-life, high receptor affinity, and improved systemic bioavailability ensure stable biological activity and patient adherence. Furthermore, unlike earlier agents such as liraglutide or exenatide, semaglutide has demonstrated more consistent metabolic and cardiovascular benefits, which may indirectly contribute to neuroprotection. Preclinical studies indicate its capacity to reduce amyloid and tau pathology, attenuate microglial activation, and improve synaptic plasticity, suggesting a potential disease-modifying role in AD.

Despite promising results, significant uncertainties remain. Existing studies vary in design, endpoints, and patient characteristics, while comparative data among GLP-1RAs are limited. Mechanistic understanding of semaglutide's central effects - including its transport across the BBB and dose-response

relationship - remains incomplete.

Novelty and relevance of this work lie in its comprehensive synthesis of recent preclinical and clinical evidence (2023–2025) focused specifically on semaglutide, rather than the GLP-1RA class as a whole. The review addresses the emerging paradigm of metabolic-neurodegenerative interaction and identifies critical knowledge gaps that hinder clinical translation - such as heterogeneity of results, insufficient human data, and methodological inconsistency. These aspects underscore the importance of re-evaluating semaglutide not only as a metabolic agent but as a candidate for disease-modifying therapy in Alzheimer's disease.

AIMS

The aim of this review is to provide a comprehensive and critical synthesis of current scientific knowledge on the role of incretin-based therapies, with a specific focus on semaglutide, in the prevention and treatment of Alzheimer's disease. The review seeks to integrate preclinical and clinical evidence, evaluate mechanistic pathways linking metabolic and neurodegenerative processes, and assess the therapeutic potential of semaglutide as a disease-modifying agent.

RESEARCH QUESTIONS

1. What preclinical and clinical evidence supports the neuroprotective and disease-modifying effects of semaglutide in Alzheimer's disease?
2. How does semaglutide differ from other GLP-1RAs in terms of pharmacological properties, BBB penetration, and central mechanisms of action?
3. What are the main metabolic, inflammatory, and neurobiological pathways through which semaglutide may influence the development and progression of Alzheimer's disease?
4. What methodological limitations and gaps exist in the current research on semaglutide and AD, and how should they be addressed in future studies?
5. What are the most promising directions for future clinical trials exploring semaglutide as a potential disease-modifying treatment for Alzheimer's disease?

MATERIALS AND METHODS

This review was conducted as a narrative evidence-based review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles. The aim was to synthesize existing evidence on the potential role of semaglutide in the prevention and treatment of Alzheimer's disease (AD), including both preclinical and clinical studies.

ELIGIBILITY CRITERIA

Studies were included if they met the following criteria:

1. investigated semaglutide specifically, or as a representative GLP-1RA, in the context of Alzheimer's disease or related neurodegenerative processes;
2. reported outcomes including at least one of the following: cognitive performance, neuroinflammation, amyloid or tau pathology, synaptic plasticity, or neuroprotection;
3. included human subjects (clinical trials or retrospective cohorts) or relevant animal/cellular models.

EXCLUSION CRITERIA:

- studies focused solely on diabetes or obesity outcomes without cognitive or neurological endpoints;
- articles not written in English;
- reviews without original data, unless providing comprehensive synthesis relevant to semaglutide's neurological effects.

SEARCH STRATEGY

Titles and abstracts were screened for relevance, followed by full-text review to assess eligibility based on predefined inclusion criteria. Additional filters included study type (e.g., preclinical, clinical trial, review) and species (human, rodent models, or human-derived organoids).

Study Types

Included studies comprised:

- Preclinical studies (animal models and cell lines) assessing cognition, neuroinflammation, and neuropathological markers.
- Clinical studies (RCTs and retrospective cohorts) evaluating semaglutide's safety, efficacy, and neuroprotective potential in humans.
- Systematic and narrative reviews summarizing preclinical and clinical evidence on semaglutide in AD.

DATA COLLECTION PROCESS

Titles and abstracts were independently screened by two reviewers. Full-text articles were retrieved for studies that met the eligibility criteria or where eligibility was unclear. Disagreements were resolved through discussion or by a third reviewer. Data extraction focused on identifying mechanistic pathways, clinical endpoints, and translational relevance. For each eligible study, the following information was collected using a standardized template: author(s), year of publication, study type, population (human, animal, or cell-based), main findings, and noted limitations. Data were organized in a comparative table (Table 1), which was used to synthesize findings across multiple dimensions: cognitive outcomes, neuropathological markers (e.g., Aβ, p-Tau), inflammatory markers, synaptic changes, and potential clinical relevance. Special attention was given to study limitations, including sample size, treatment duration, lack of placebo control, or translational gaps between preclinical and clinical findings. The analysis was qualitative in nature and did not include a statistical meta-analysis. This method allowed for both qualitative and semi-quantitative synthesis of the current landscape of semaglutide research in AD. Ongoing and registered clinical trials were also documented to capture emerging evidence and identify gaps in the literature.

PRISMA SUMMARY

The PRISMA flow diagram is not presented; no quantitative synthesis or pooled statistical analysis was performed.

Identification: Records identified through database searching (PubMed, Google Scholar): n = 427. Additional records identified through manual search of references and gray literature: n = 12. Total records identified: n = 439.

Screening: Records after duplicates removed: n = 386. Records screened (titles and abstracts): n = 386. Records excluded (irrelevant outcomes, no mention of semaglutide, non-AD focus): n = 302.

Eligibility: Full-text articles assessed for eligibility: n = 84. Full-text articles excluded (not meeting inclusion criteria, insufficient data, language other than English): n = 39.

Included in Review: Studies included in qualitative synthesis (Table 1): n = 16. Preclinical studies: n = 7. Clinical studies (RCTs and cohorts): n = 5. Reviews and systematic reviews: n = 4.

INCLUDED STUDIES

A total of 16 studies were included in the qualitative synthesis (see Table 1). These comprised:

- 7 preclinical studies involving animal models and cell lines, primarily investigating semaglutide's effects on cognition, neuroinflammation, and neuropathological markers in Alzheimer's disease models.
- 5 clinical studies, including randomized controlled trials (RCTs) and retrospective cohort studies, focusing on semaglutide's safety, efficacy, and potential neuroprotective effects in humans with or at risk of Alzheimer's disease.
- 4 systematic and narrative reviews summarizing existing preclinical and clinical evidence on semaglutide's impact on AD pathology and cognitive outcomes.

The distribution of study types reflects the early and evolving stage of clinical research on semaglutide in neurodegenerative diseases, emphasizing the need for further well-designed trials to confirm and expand current findings.

RESULTS

PRECLINICAL STUDIES

Animal models consistently demonstrated that semaglutide improves cognitive function, reduces neuroinflammation and oxidative stress, and modulates key pathological markers of Alzheimer's disease, including beta-amyloid and tau pathology. For example, Zhao-Jun Wang et al. (2023) and Elbadawy et al. (2025) reported improvements in memory and reductions in tau and neuroinflammation. Meca et al. (2024) highlighted enhanced autophagy and reduced apoptosis, while Boboc et al. (2024) showed improvements in cognition and anxiety, though motor effects were minimal. One study by Germano et al. (2024) observed no significant cognitive or pathological benefit, suggesting that dose, duration, or administration route may critically influence outcomes. Overall, preclinical studies indicate robust neuroprotective effects, but variability in experimental protocols, treatment lengths, and dosages limits direct comparability and translational confidence.

CLINICAL STUDIES

Human trials remain limited and largely exploratory. Retrospective cohort studies (Wang et al., 2024; De Giorgi et al., 2024; Siddeeque et al., 2024) consistently observed a lower incidence of Alzheimer's disease or cognitive decline among semaglutide users, indicating a potential protective effect. Double-blind trials (Koychev et al., 2024) and large-scale RCTs (Cummings et al., 2025) are ongoing, but results are not yet available, highlighting the need for long-term, adequately powered studies to confirm efficacy.

REVIEW STUDIES

Systematic and narrative reviews (Au et al., 2025; Tipa et al., 2024; Chen et al., 2024; Wang et al., 2023) integrate preclinical and clinical evidence, consistently reporting trends of cognitive improvement, reduced neuroinflammation, and decreased beta-amyloid and tau pathology. Reviews emphasize that while preclinical evidence is compelling, human data remain sparse and heterogeneous, underscoring unresolved questions regarding dosing, blood–brain barrier penetration, and class-specific versus drug-specific effects among GLP-1 receptor agonists.

Across study types, semaglutide demonstrates strong biological plausibility as a neuroprotective agent. Preclinical models show reproducible improvements in neuropathological and cognitive endpoints, yet translation to humans is limited by small sample sizes, short treatment durations, and heterogeneity in outcome measures. Contradictory findings, such as those reported by Germano et al. (2024), highlight the importance of dose, administration route, and experimental design in influencing results. Retrospective human studies suggest potential disease-modifying effects, but causality cannot be confirmed due to observational designs. Collectively, the data suggest promising trends that warrant further investigation in well-designed, long-term, placebo-controlled clinical trials incorporating standardized cognitive and biomarker endpoints. Table 1 summarizes study designs, populations, interventions, and key findings, providing a structured overview of reproducibility, effect trends, and limitations across preclinical and clinical studies.

Table 1. Research on the Impact of Semaglutide in Alzheimer's Disease

Author(s)	Year	Study Type	Population	Sample Size	Treatment Duration	Dosage	Outcome Measures	Key Findings	Limitations
Au et al. [22]	2025	Systematic review	Humans and animal models	6-30	4-12 weeks (average 8)	10 – 25 (nmol/kg)	Weight loss, BMI reduction,waist circumference, metabolic parameters, cognitive function (e.g., memory tests), motor function, neuroinflammation markers, amyloid/ tau biomarkers, quality of life	Improves cognition, motor function; reduces neuroinflammation & oxidative stress	Few clinical studies; long-term safety unknown
Zhao-Jun Wang et al. [23]	2023	Preclinical study	Animal models	50 transgenic mice; 50 wild mice	30 days	Not specified	Behavioral test; brain glucose metabolism; molecular/ biochemical markers (e.g., expression of SIRT1 and GLUT4, Aβ, tau, GOD-POD, HK)	Improves cognition and glucose metabolism	Animal data only; clinical confirmation needed
Meca et al. [24]	2024	Review + Experimental Data	Animal models	Not specified	Not specified	Not specified	Cell viability, apoptosis inhibition, autophagy enhancement, SIRT1/GLUT4 pathway activation, amelioration of Aβ and Tau pathology,	Reduces apoptosis, inflammation; improves autophagy and neuroprotection	Animal-based; mechanisms unclear

							reduction of neuroinflammation		
Zhang et al. [25]	2024	Experimental study	Animal models & human AD organoids	12 mice/ group; 3 organoids/ group	6 months (mice); 5 days (organoids)	~12,16 (0,05 mg/ kg/day)	Morris Water Maze, Barnes Maze, Nest building, Active avoidance test, Brain histology and biochemistry, cell viability, morphology/ surface area	Improves memory; reduces Aβ, p-Tau, neuroinflammation	Preclinical; limited translation to humans
Wang et al. [26]	2023	Review	Humans and animal models	Not specified	Not specified	Not specified	Neuroprotection/ synaptic function, amyloid and Tau pathology, neuroinflammation, neurogenesis/ growth factor	Improves cognition; reduces neuroinflammation & Aβ pathology	Mixed evidence; limited clinical data
Wang et al. [27]	2024	Retrospective cohort	Humans without AD diagnosis	Not specified	Up to 3 years	Not specified	First-time AD diagnosis; AD-related medications	Lower risk of new AD diagnosis	Short follow-up; safety unknown
Germano et al. [28]	2024	Experimental study	Animal models	Not specified; Up to 5 mice per cage	6-7 weeks	10-25	Behavior (Open field, Novel Object recognition, Morris Water Maze), histology/ biochemistry (Thioflavin S, IBA1, GFAP), qPCR in hippocampus)	No cognitive or pathology improvement	Animal study; possible insufficient dose/duration
Chen et al. [29]	2024	Review (preclinical and clinical)	Preclinical models and clinical populations with AD	No data	No data	No data	No data	Reduces neuroinflammation, oxidative stress; improves synaptic function	Mainly preclinical data
Cummings et al. [30]	2025	Phase 3 RCT	Humans with early-stage AD	3680 (1840 per trial)	156 weeks (104-week main phase, 52-week blinded extension, 5-week follow-up washout	3 mg OD (weeks 0–4) → 7 mg OD (weeks 4–8) → 14 mg OD thereafter	CDR-SB score, ADCS-ADL-MCI score, time to progression to CDR global ≥ 1.0, Plasma: NfL, p-tau181, GFAP, hs-CRP	Ongoing evaluation of semaglutide's disease-modifying effects	No results yet; long-term effects unknown
Boboc et al. [31]	2024	Preclinical study	Animal models	20 total (5 per group × 4 groups)	28 days	0,1 mg/kg	Blood glucose, body weight, behavioral tests, Open Field Test, Novel Object Recognition Test, Social Chamber Test, 0-Maze Test,	Improves cognition and anxiety; no motor effect	Small sample; short treatment
Abdulhameed et al. [32]	2024	Preclinical study	Animal models	Not specified	30 minutes	1×106 cpm/ mouse (delivered in per naris, bilaterally)	%Inj/g (percent of injected dose per gram of brain tissue), %Inj/ml (percent of injected dose per of serum), %Precip (percentage of radioactivity precipitated by TCA)	Minimal effect via nasal administration	Animal study; limited administration route
Koychev et al. [33]	2024	Double-blind placebo RCT	Humans	Up to 88 individuals	52 weeks	3mg 14mg (gradually up-titrating over the first 8 weeks)	The 1-year change in tau PET signal; TSPO PET; AD biomarkers measured in blood (at weeks 4, 8, 26, 39, and 52); cognitive assessments (at weeks 26 and 52)	Possible reduction in tau and neuroinflammation; trial ongoing	Small sample size; no results yet

De Giorgi et al. [34]	2024	Retrospective propensity cohort	Humans	Not specified	Primary analysis 1 year; secondary analysis 2 year	Not specified	Risk of diagnosis of 22 neurological and psychiatric outcome; Risk of 15 Negative Control Outcomes (NCOs); All-cause mortality	Lower risk of cognitive deficits and dementia	Observational design; no direct AD diagnosis
Siddeeque et al. [35]	2024	Large-scale retrospective cohort	Humans	Not specified; study utilized 152 398 854 patient records from EHR networking	Not specified; data were collected between January 1, 2010, and December 31, 2023	Not specified	Incidence of 4 major neurodegenerative disorders; All−cause mortality; incidence of 12 other neurodegenerative disorders	Reduced AD risk; suggested neuroprotection	Observational study; causality not confirmed
Elbadawy et al. [36]	2025	Preclinical study	Animal models	40 mice	Not specified	Not specified	Hippocampal ACE2/Ang1-7 patway, autophagy /SIRT1/FOX01, microglial polarization	Improved cognition; reduced tau; modulated neuroinflammation	Animal data; short treatment duration
Tipa et al. [37]	2024	Systematic review	Animal models and cell lines	N/A	N/A	N/A	Cognitive performance, neurobiological markers, metabolic and inflammatory parameters, cell viability and apoptosis, brain structural and functional alterations	Neuroprotective, antiapoptotic; improved cognition and reduced neuronal damage	Few studies; no human data; limited databases

COMPARATIVE INTERPRETATION

When comparing across all three categories:

- Preclinical studies provide strong mechanistic and functional evidence that semaglutide exerts neuroprotective, anti-inflammatory, and cognition-enhancing effects.
- Clinical studies offer early signals of similar benefits in humans—particularly in terms of reduced disease risk and biomarker improvement—but the findings are not yet conclusive.
- Review studies synthesize these data, emphasizing the biological plausibility of semaglutide's role in neuroprotection, while underscoring the limited number and small scale of human trials to date.

Thus, while preclinical and review data robustly support semaglutide's potential as a disease-modifying agent, clinical validation remains ongoing. The translational gap between animal and human findings highlights the need for longitudinal RCTs with adequate power and biomarker endpoints to determine whether semaglutide can truly alter the course of Alzheimer's disease.

In the context of semaglutide research:

Preclinical studies achieve high statistical significance, but clinical relevance remains hypothetical.

Clinical studies so far show potentially meaningful trends, but few reach statistical significance, and none yet demonstrate clinically significant improvement in Alzheimer's symptoms or progression.

Overall, the preclinical evidence strongly supports semaglutide's neuroprotective action at a statistical level, suggesting mechanistic plausibility.

The clinical evidence, though promising, is still inconclusive both statistically and clinically.

Review papers unify these findings, highlighting a consistent biological rationale but emphasizing the gap between experimental significance and real-world efficacy [22-37].

DISCUSSION

This section discusses the mechanistic background and current evidence regarding the neuroprotective potential of semaglutide in Alzheimer's disease. The discussion integrates preclinical and clinical findings to identify consistent trends, limitations, and directions for further research.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, leading to impairments in memory, cognition, behavior, and daily functioning [10,11]. Its etiology is multifactorial, involving beta-amyloid plaques, tau tangles, altered neuronal signaling, and metabolic dysfunction. Chronic neuroinflammation, mediated by microglia and astrocytes, contributes to synaptic dysfunction and neuronal loss. Impaired brain insulin signaling and glucose metabolism exacerbate neurodegenerative processes, while mitochondrial dysfunction increases oxidative stress and further damages neurons. These interconnected mechanisms create a vicious cycle of metabolic and neurodegenerative pathology, providing a rationale for exploring metabolic-targeted therapies in AD [12,13].

SEMAGLUTIDE

Semaglutide, a long-acting synthetic glucagon-like peptide-1 receptor agonist (GLP-1RA), originally approved for type 2 diabetes, modulates multiple pathways relevant to neurodegeneration [17-19]. Activation of GLP-1 receptors in the brain engages intracellular signaling cascades (e.g., PI3K/Akt, MAPK) that influence neuronal survival, synaptic function, and anti-apoptotic mechanisms. Preclinical studies demonstrate that semaglutide reduces microglial activation, supports autophagy, improves mitochondrial function, and mitigates oxidative stress. Its extended half-life allows weekly subcutaneous administration, facilitating adherence in potential long-term trials [20-23].

SEMAGLUTIDE IN ALZHEIMER'S DISEASE

1. Crossing the BBB, enabling direct action in the brain and the entire central nervous system.
2. Activation of GLP-1 receptors in the brain (primarily in the hippocampus and cerebral cortex, areas involved in cognition, learning, and memory).
3. Improvement and support of mitochondrial function: increased ATP production, reduced oxidative stress, and support for cellular energy metabolism.
4. Reduction of neuroinflammation: inhibition of microglial activation and reduced release of proinflammatory cytokines (e.g., IL-1β, TNF-α).
5. Support for autophagy: improved clearance of misfolded proteins, such as beta-amyloid and hyperphosphorylated tau protein.
6. Inhibition of neuronal apoptosis: activation of cell survival pathways (e.g., PI3K/Akt), protection of neurons from degeneration.
7. Improvement of synaptic plasticity: strengthening neuronal connectivity and improving cognitive function.
8. Reduction of brain insulin resistance: improvement of glucose metabolism in neuronal structures, protection against metabolic dysfunctions associated with Alzheimer's disease (the "type 3 diabetes" hypothesis) [20,21].

In preclinical studies, it affects mitochondrial function, autophagy, microglial activation, and oxidative stress. However, translation to human cognitive outcomes remains uncertain, with limited clinical trials confirming direct neuroprotective effects.

DISCREPANCIES BETWEEN PRECLINICAL AND CLINICAL FINDINGS

While preclinical models consistently show cognitive improvement, reduced amyloid and tau pathology, and lowered neuroinflammation, translation to human studies remains limited. Early clinical trials and observational studies indicate potential neuroprotective effects, but findings are heterogeneous and often underpowered. For example, Germano 2024 reported minimal cognitive benefit despite improvements in metabolic parameters, highlighting possible discordance between mechanistic effects and measurable clinical outcomes. Differences in species, disease stage, dosing regimens, and duration may partly explain these discrepancies.

CRITICAL CONSIDERATIONS AND LIMITATIONS

Contradictory results, including those from Germano 2024 [28], emphasize the need to critically examine study design and endpoints. Short treatment durations, small sample sizes, and reliance on surrogate markers may underestimate the potential cognitive benefits of semaglutide. In addition, the uncertainty surrounding blood–brain barrier (BBB) penetration and central exposure raises questions about dose adequacy in human studies. The lack of standardized cognitive and biomarker endpoints further complicates interpretation.

LIMITATIONS OF EXISTING RESEARCH

Current evidence is limited by several factors:

- small sample sizes and short intervention periods in both preclinical and clinical studies;
- predominant reliance on surrogate metabolic or neuropathological outcomes rather than direct cognitive endpoints;
- absence of long-term, placebo-controlled trials in humans;
- heterogeneity in study populations, including metabolic status, genetic risk factors (e.g., APOE4), and comorbidities;
- limited comparative data between semaglutide and other GLP-1RAs, making it difficult to discern drug-specific versus class effects.

FUTURE RESEARCH DIRECTIONS

Future investigations should stratify patients by metabolic status and genetic background, including APOE4 carriage and degree of insulin resistance. Optimizing dosing strategies, exploring alternative delivery routes (such as intranasal or nanocarrier-based systems), and developing biomarkers for treatment response are crucial next steps. Furthermore, long-term placebo-controlled trials with standardized cognitive and neuroimaging outcomes are required to validate the therapeutic potential of semaglutide in AD.

Collectively, current data support semaglutide as a biologically plausible and clinically promising candidate for Alzheimer's disease modification. Nevertheless, the strength of evidence remains preliminary, and well-designed, long-term, placebo-controlled clinical trials are required to determine its therapeutic validity and safety in neurodegenerative populations.

Overall, preclinical evidence supports a biologically plausible neuroprotective role for semaglutide, but current clinical data are insufficient to confirm efficacy in AD. Addressing methodological limitations, standardizing endpoints, and carefully selecting patient populations will be essential to translating preclinical promise into meaningful therapeutic outcomes.

CONCLUSIONS

CONFIRMED EFFECTS AND SUPPORTING EVIDENCE

Preclinical studies consistently demonstrate that semaglutide improves cognitive function, reduces neuroinflammation and oxidative stress, and attenuates β-amyloid and tau-related neuropathology. Evidence from early clinical studies suggests potential neuroprotective effects, although data remain limited. Semaglutide's dual action on metabolic and neurodegenerative processes provides a biologically plausible mechanism supporting its therapeutic potential in Alzheimer's disease. Its safety profile in type 2 diabetes further supports potential repurposing for neurodegenerative conditions.

UNRESOLVED QUESTIONS AND GAPS IN CURRENT KNOWLEDGE

Current evidence is preliminary and largely exploratory. Key gaps include limited long-term human data, uncertainty regarding optimal dosing and administration routes, and unclear extent of BBB penetration. It remains unresolved whether the observed benefits are specific to semaglutide or reflect a class effect of GLP-1RAs. Mechanistic understanding of central effects, patient stratification by metabolic status or genetic profile (e.g., APOE4), and predictors of therapeutic response require further investigation.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future studies should focus on long-term, placebo-controlled clinical trials with standardized cognitive and biomarker endpoints. Research should evaluate different dosing strategies, alternative delivery routes, and comparative efficacy among GLP-1RAs. Patient stratification by metabolic and genetic factors, as well as identification of predictive biomarkers, will be critical to personalizing therapy. Integration of metabolic and neuroprotective outcomes in trial design is recommended to capture the full therapeutic potential of semaglutide in Alzheimer's disease.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

Honorata Derlatka conceptualized the study and designed the methodology. Łukasz Skowron, Honorata Derlatka, Bartłomiej Bobrowski, Jan Drugacz, Olaf Helbig, Klaudia Kontek, Anna Kukhtiak, Julia Marcinkowska and Martyna Radelczuk performed the literature review and data extraction. Łukasz Skowron and Honorata Derlatka drafted the manuscript.

All authors critically revised the manuscript and approved the final version.

USE OF AI

AI tools were used to assist with language editing during manuscript preparation. The authors reviewed and approved all content.

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