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Review Article

Systematic evaluation of the effects of exenatide and liraglutide on neurodegenerative diseases induced by type 2 diabetes mellitus

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Abstract

Currently, there are no effective treatment methods for Alzheimer's disease (AD), Parkinson's disease (PD), and olfactory dysfunction (OD). Given common pathophysiological features of neurodegenerative diseases such as AD and type 2 diabetes mellitus (T2DM), antidiabetic drugs such as exenatide and liraglutide, which act as incretin mimetics, are tested as a potential treatment option. This systematic review aimed to evaluate the effects of exenatide and liraglutide pharmaceuticals on amyloid-beta (Aβ)/tau protein and cognition in patients with AD, PD, OD, and concomitant T2DM. Randomized controlled clinical trials were retrieved from electronic databases using a combination of relevant MeSH keywords, and the retrieved studies were evaluated. Results were presented as the number in the relevant date range. No randomized, controlled, clinical trial in which exenatide or liraglutide was administered to patients with PD and T2DM was found**.** Four studies that examined the effects of these two drugs on patients with T2DM and PD were retrieved. One study that investigated the effects of exenatide or liraglutide on patients with T2DM and OD was extracted. Currently, there are no incretin mimetics agents that can improve the pathophysiology of neurodegenerative diseases such as AD, PD, OD, and concomitant T2DM and that can be used in the treatment of these diseases. For these pharmacological agents to be included in the routine treatment algorithm of neurodegenerative diseases accompanied by T2DM, further multicenter, randomized clinical trials including a larger number of cases are needed

Keywords: Alzheimer's Disease, Brain, Exenatide, Glucagon-Like Peptide 1, Liraglutide

Introduction

Type 2 diabetes mellitus (T2DM) is a disease that negatively affects almost all tissues and imposes a serious socio-economic burden on the health system due to complications secondary to its chronic effects [1]. Alzheimer's disease (AD) and T2DM are characterized by epidemiological, histopathological, molecular, and biochemical abnormalities, and the prevalence of T2DM leading to AD has reached 70% with uncontrolled hyperglycemia [2].

T2DM predisposes to neuropathophysiological changes, including oxidative stress, and triggers inflammatory responses in the brain that result in cognitive impairment [3]. Insulin resistance is often associated with T2DM and can induce defective insulin pathways and intercellular communication in the central nervous system. In addition, insulin resistance increases the risk of cognitive function loss in the elderly [1,4]. Targeting cellular mitochondrial biogenesis and mitophagy pathways with the use of mitochondrial RNAs may be a powerful therapeutic strategy for T2DM-associated AD. Anti-T2DM drugs against AD are among the promising treatment strategies [5].

Glucagon-like peptide-1 (GLP-1) is an incretin hormone and, as within its GLP-1 analogs, it activates insulin secretion and is used in the treatment of T2DM. GLP-1 and GLP-1 analogs increase synaptic plasticity and restore cognitive deficits in neuronal dysfunction and/or degeneration models [6]. The beneficial effects of exenatide on short- and long-term memory performances are driven by increasing the brain's anaerobic glycolysis [4].

Therefore, the GLP-1 analog exenatide, which has neuroprotective effects, and the GLP-1 analog liraglutide, which provides a longer-lasting effect by binding to the same receptor with GLP-1, have been investigated in the treatment of many neurodegenerative diseases, including Olfactory dysfunction, especially AD, and Parkinson's disease (PD) [6-9]. Novel treatment modalities for AD have been investigated, specifically targeting brain insulin resistance. Among the promising pharmacological agents, incretin receptor agonists, and antidiabetics, which suppress glucagon secretion while increasing glucose-dependent insulin secretion, have taken the first place.

GLP-1 is a peptide hormone belonging to the incretin family, derived from the tissue-specific post-translational processing of the proglucagon peptide. This peptide hormone is secreted from the nucleus tractus solitarius in the brainstem and from L-cells in the small intestine, which results in glucose-dependent insulin secretion.

This systematic review aimed to evaluate exenatide and liraglutide, incretin mimetics drugs, which are used in the treatment of patients with T2DM-induced neurodegenerative disease.

Materials and Methods

This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10,11].

Literature search strategy, inclusion, and exclusion criteria

A comprehensive and systematic literature search of numerous electronic databases, including Web of Science, Medline, Central Embase, and Scopus, was performed. A combination of keywords was used to retrieve studies broadly associated with the topic of interest. The search criteria were as follows: "Type 2 diabetes mellitus", "brain", "Glucagon-like peptide-1", "exenatide", and "liraglutide". "Alzheimer's Disease", "Olfactory dysfunction" or "Parkinson's Disease".

In the first stage of screening, titles and abstracts were screened for relevant studies. Subsequently, the full texts were downloaded and assessed for eligibility. This process was carried out independently by three researchers (IY, NK, and BB). The percentage distribution of articles by year was recorded. Of all the studies, those with high evidential levels were selected. The study of Lijmer et al. was used to determine the level of evidence of the studies [12,13].

Bias risk was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2) [14].

The full texts of the articles were reviewed and disagreements among the authors were resolved by consulting senior. After the reference lists of the studies that were decided to be examined were manually scanned, the inclusion criteria of the studies were classified as follows:

- Studies published in English.
- Randomized controlled trials evaluating the effect of GLP-1 in T2DM-induced neurodegenerative diseases.
- Randomized controlled trials evaluating drugs with incretin mimetics in T2DM-induced neurodegenerative diseases.
- Randomized controlled trials evaluating exenatide or liraglutide in T2DM-induced neurodegenerative diseases.
- Randomized controlled trials evaluating the effect of GLP-1 in T2DM-induced AD, olfactory dysfunction, or PD.
- Randomized controlled trials evaluating drugs that act incretin mimetics in T2DM-induced AD, olfactory dysfunction, or PD.
- Randomized controlled trials evaluating exenatide or liraglutide in T2DM-induced AD, olfactory dysfunction, or PD.

The exclusion criteria:

- Randomized and non-clinical studies.
- Comments, letters to the editor, protocols, guidelines, systematic reviews, and studies with meta-analysis.
- Accepted but not published studies.
- Research published in non-scientific electronic databases.
- Case reports.

Data analysis

Data on patients treated with exenatide were extracted through a literature search on electronic databases. All articles included in the systematic review were prepared using a pre-made checklist. The checklist comprises the title of the article, the name of the first author, the year of publication, the place of study, number of cases, patient sex, patient age, diagnosis of neurodegenerative disease in addition to T2DM, which GLP-1 analog is used and their doses, administration times and the tests performed after GLP-1 application.

Statistical analysis

The statistical analyses were performed using *Microsoft Office Excel*. The results were presented as numbers.

Results

4,667 studies were retrieved using the keywords T2DM and brain. Of these studies, 203 were randomized controlled trials. 110 studies were found using the keywords T2DM, brain, and GLP-1 analogs. 68 studies were extracted using the keywords T2DM, brain, and exenatide; 26 studies were found using the keywords T2DM, brain, GLP-1 analog, and exenatide. 24 studies were retrieved using the keywords T2DM, brain, exenatide, and AD. 12 studies were found using the keywords T2DM, brain, exenatide, and PD (**Table 1**).

No clinical trial or randomized clinical trial was found regarding the effect of exenatide on neurodegenerative changes in patients with T2DM and concomitant neurodegenerative diseases. Four studies [15-18] including clinical trials or randomized clinical trials, were found on the effect of liraglutide on neurodegenerative changes in cases diagnosed with T2DM, which were related to AD. No studies related to exenatide were found during the electronic database search; however, patients treated with exenatide were encountered in a study related to liraglutide [19]. In another study, olfactory dysfunction [19], a neurodegenerative disease, was investigated instead of AD (**Table 2**).

Discussion

In uncontrolled T2DM cases, the cerebral tissue is affected at the cellular level, and accordingly, memory-related learning disorders

Table 1: Distribution of studies per year.

Keywords	Case report (amount)	Clinical trial (amount)	Randomized-controlled trial (amount)	Meta-Analysis (amount)	Systematic review (amount)	Distribution by years	Total number of studies (amount)
Brain	157763	51012	25104	9178	11915	1784-2023	2,173,426
AD	3750	5037	2921	1729	2072	1913-2022	183286
PD	8053	6010	2778	1226	1706	1812-2022	139834
OD	328	277	127	76	144	1964-2022	8015
T2DM	7228	17915	13743	3947	3583	1951-2022	173847
GLP-1	232	2052	1694	393	360	1978-2022	17456
EXN	89	401	338	111	94	1992-2022	3606
LIR	114	487	436	148	135	2001-2022	3576
AD+T2DM	18	22	12	17	0	1987-2022	1898
PD+T2DM	13	5	3	12	7	1987-2022	413
OD+T2DM	2	1	1	1	1	1991-2022	30
AD+T2DM+ GLP-1	0	2	1	0	1	2002-2022	139
PD+T2DM+ GLP-1	0	0	0	0	0	2009-2022	13
OD+T2DM+ GLP-1	0	1	1	0	0	2016-2022	3
AD+T2DM+EXN	0	0	0	0	1	2002-2022	30
PD+T2DM+EXN	0	0	0	1	0	2009-2022	17
OD+T2DM+EXN	0	1	1	0	0	2016-2022	2
AD+T2DM+LIR	0	0	0	0	0	2009-2022	34
PD+T2DM+LIR	0	0	0	0	0	2012-2022	15
OD+T2DM+LIR	0	0	1	0	0	2019	1

T2DM: Type 2 Diabetes Mellitus; GLP-1: Glucagon-like Peptide-1; EXN: Exenatide; LIR: Liraglutide; AD: Alzheimer's Disease; OD: Olfactory Dysfunction; PD: Parkinson's Disease

Table 2: Studies that met the research criteria and were included in the research.

Publications trials registration (ClinicalTrials.gov record) and/or study design [18]	Neuro-degenerative diseases	Exatinide dose and duration (Patient number)	Liraturide dose and duration (Patient number)	Change from baseline at study end, GLP-1RAs versus comparator		
				Tau	Amiloid-β	Cognition
NCT01469351, randomized, placebo-controlled, double-blinded trial [15]	AD	-	Finally, 1.8 mg subcutaneously daily for, 6 mounts (n=20)	-	-	-
NCT01469351, randomized, placebo-controlled, double-blinded trial [16]	AD	-	Finally, 1.8 mg subcutaneously daily for, 26 weeks (n=18)	-	-	Cognition increased signifcantly with treatment in the liraglutide group

Randomized, placebo-controlled, double-blinded trial [17]	AD	-	Finally, 1.8 mg subcutaneously daily for, 12 weeks (n=25)	-	-	No cognitive differences found after liraglutide treatment compared to placebo
Randomized, controlled trial [19]	Olfactory dysfunction	Finally, subcutaneously 10 mg twice daily within 2 weeks (n=10)	Finally, subcutaneously 1.8 mg daily for, within 2 weeks (n=9)	-	-	GLP-1Ras ameliorated cognitive and olfactory abnormalities in obese subjects
NCT01843075, randomised, double-blind, placebo-controlled, phase IIb trial [18]	AD, Dementia	-	Finally, subcutaneously 1.8 mg daily for, 12 mounts (n=103)	Reduction in tau formation	Reduction and change in amyloid levels	-

may be seen [20]. In addition, metabolic disorders, impaired oxidative phosphorylation, and mitochondrial dysfunctions play a role in the physiopathology of damage at the cellular level in both AD and T2DM cases [2]. Uncontrolled hyperglycemia affects cerebral tissues by increasing the dysregulation of signaling pathways involved in the pathophysiology of mitochondrial dysfunctions in cases with T2DM [2].

GLP-1 receptors exist in the cerebral cortex, hypothalamus (ventromedial hypothalamus, arcuate nucleus, paraventricular nucleus), hippocampus, thalamus, amygdala, and basal ganglia. GLP-1 receptors are also present in the NTS, lateral geniculate nucleus, dorsal vagal complex, and area postrema [21]. GLP-1, which has such a widespread cerebral receptor distribution, regulates glucose metabolism and affects neurological and cognitive functions.

The effects of GLP-1 on cerebral tissue metabolism and functions have recently been investigated. Peripheral neuropathy often develops in uncontrolled type 2 and type 1 diabetic patient. In addition, atrophy is observed in the grey matter areas and cerebral areas related to somatosensory perception. Atrophies are also observed in various cortical and subcortical cerebral fields in T2DM patients. HBA1c is associated with cognitive dysfunction. The incidence of AD, olfactory dysfunction, and PD neurodegenerative diseases increase in T2DM patients. Cardiovascular changes such as endothelial destruction, ventricular dysfunction, and atherosclerosis are also effective in the deterioration of cognitive functions. In addition, GLP-1 receptors are present in the central and peripheral nervous systems [22].

Exenatide, which can be used together with drugs containing metformin, a thiazolidinedione, basal or long-acting insulins, or one or more drugs used in the treatment of T2DM containing sulfonylureas, belongs to incretin mimetics drugs. Administration of liraglutide in preclinical models reduces amyloid-β deposition and neuroinflammation [23], and improves brain glucose metabolism [24], and cognitive outcomes [25]. GLP-1RA drugs have also been investigated in cerebral neurodegeneration.

The pharmacokinetics of liraglutide have been studied in patients with renal and hepatic impairment and did not raise any safety concerns. The effects of age and gender on liraglutide pharmacokinetics have been investigated and it has been reported that all participants, regardless of age or gender, can use liraglutide in the usually recommended dosing regimen [26]. Liraglutide is slowly absorbed and has a half-life of approximately 13 h. It can be safely administered at any time of the day and by subcutaneous injection once a day, regardless of meals [27].

The effects of liraglutide on neurodegeneration, blood flow, and cognition were evaluated in patients with AD aged 50-80 years who were treated with liraglutide (n = 20) or placebo (n = 20) for six months [15]. The controlled, randomized double-blinded study examined changes in an amyloid-β deposition in the central nervous system. In addition, cognition assessment was carried out using neuropsychological testing. Changes in glucose uptake in the central nervous system were examined through 18F-fluorodeoxyglucose positron emission tomography, and contrast-enhanced perfusion-weighted magnetic resonance imaging was used to evaluate cerebral perfusion [15]. The following dosing regimen was used for patients with AD; Liraglutide dose: initially, 0.6 mg subcutaneously daily for one week; hereafter 1.2 mg daily for one week before finally increasing to 1.8 mg daily after another week. The most common adverse events reported in patients treated with liraglutide were gastrointestinal disturbances, mostly mild to moderate transient nausea. No pharmaceutical preparation approved in the pharmaceutical industry could improve cognition function by reducing the accumulated amyloid-β plaques in cases with AD and T2DM [15]. A study has suggested that glucose transporters become a potential treatment target because there are fewer glucose transporters than normal in the blood-brain barrier in AD and the reduced expression of these transporters exacerbates the symptoms of AD. In that study, the incretin hormone GLP-1 analog liraglutide has been tested [16] and proposed that GLP-1 analogs may help in relieving the symptoms of AD by preventing the decrease of cerebral metabolic rate for glucose and increasing the number of glucose transporters [16].

In a randomized, placebo-controlled, double-blind trial, 38 patients with AD were treated with liraglutide (n = 18) or placebo (n = 20) for 6 months, and the blood-brain glucose transfer capacity in the two groups and healthy age-matched control group (n = 6) were determined [16]. Brain metabolism was evaluated using Michaelis-Menten analysis and fluorodeoxyglucose positron emission tomography. A cognition examination was performed using the Wechsler Memory Scale. Liraglutide treatment, compared to placebo, significantly raised the blood-brain glucose transfer

capacity of the cerebral cortex from 0.72 to 1.1 umol/g/min, equal to that in healthy volunteers [16].

In a double-blind, placebo-controlled study, insulin resistance was reported to be a metabolic condition before the development of neurodegenerative disorders, including T2DM, cardiovascular disease, and AD [17]. The neural effects of liraglutide, a GLP-1 agonist, (11 placeboes, 19 liraglutide) administered to cognitively normal late middle-aged individuals with subjective cognitive complaints were evaluated. All participants underwent neuropsychological testing before and after 12 weeks of liraglutide or placebo administration (Week 1: Subcutaneous morning dose of 0.6 mg, Week 2: Subcutaneous morning dose of 1.2 mg, and Week 3 and for the duration of study: Subcutaneous morning dose of 1.8 mg) [17]. After 12 weeks of treatment with an active drug or placebo, participants returned for a follow-up visit, in which the OGTT, cognitive testing, and MRI scans were repeated [17]. There was a significant improvement in intrinsic connectivity in the active study group compared to the placebo group within the default mode network, but there was no measurable cognitive difference [17]. The authors reported that larger and longer-term studies are needed to determine whether liraglutide has neuroprotective benefits in individuals at risk for AD [17].

Another study investigated the therapeutic effects of GLP-1 Ras on psychological behaviors and olfactory networks [19]. Cognitive, olfactory, and odor-induced brain activation assessments were performed on 35 obese, 35 non-obese, and 35 control subjects, matched for age, sex, and education, with T2DM. Among the participants, GLP-1Ra was administered for 3 months to 20 obese patients with T2DM who had poor glycemic control and received metformin monotherapy and were re-evaluated in terms of metabolic, cognitive, olfactory, and neuroimaging changes [19]. The Montreal Cognitive Assessment score and the olfactory test total score of obese diabetic subjects treated with GLP-1Ra for 3 months were evaluated. Odor-induced left parahippocampus activation was observed after measurements were performed in the bilateral parahippocampus, amygdala, piriform cortex, insula, orbitofrontal cortex, and hippocampus through the odor-induced functional magnetic resonance imaging [19].

In preclinical studies using transgenic AD models, liraglutide has been extensively investigated in AD, as it exerts neuroprotective effects by reducing amyloid oligomers, normalizing synaptic plasticity, and cerebral glucose uptake, and increasing the proliferation of neuronal progenitor cells [18].

Since AD is an important cause of morbidity and its treatment is only symptomatic, its treatment modalities have been examined in many studies. In a study, liraglutide, a GLP-1 analog approved for the treatment of patients with T2DM and obesity, was tested. In that multicenter, randomized, double-blind, placebo-controlled study, a total of 206 volunteers including AD cases with mild dementia were given either placebo or liraglutide (all participants started treatment with a dose of 0.6 mg, which was increased to 1.8 mg within 4 weeks) [18]. Changes in cerebral glucose metabolic rate in the hippocampus, medial temporal lobe, and posterior cingulate regions were evaluated through 18F-fluorodeoxyglucose positron emission tomography in patients receiving liraglutide treatment compared to the placebo group. In addition, neurophysiological clinical, and cognitive measurements related to AD were performed. Using magnetic resonance spectroscopic imaging and translocator protein positron emission tomography, the microglial activations of the cases were evaluated, and the changes in the levels of the proteins were assessed using tau and amyloid imaging. Pro-inflammatory and anti-inflammatory cytokines, plasma markers of pharmacodynamic neuroinflammation, were compared across groups. The outcomes obtained suggested that liraglutide and GLP-1 analogs may represent an important class of compounds that will be further evaluated in clinical trials for the treatment of AD [18].

In this systematic review, randomized clinical trials extracted from electronic databases were evaluated. It is an undeniable fact that exenatide and liraglutide, which are GLP-1 analogs and act as incretin mimetics, hold potential promise in the treatment of neurodegenerative diseases such as T2DM-induced AD and OD.

This systematic evaluation also has some limitations. The first limitation includes the followings; the medical histories of the cases included in the studies were different, including many factors such as T2DM and cognition levels; systemic additional pathologies affecting the neurodegenerative process were ignored; radiological evaluations could not be standardized; limited radiological examinations were performed and only a limited area of the cerebral tissue was evaluated; the time elapsed from the first diagnosis of neurodegenerative pathology and/or T2DM was ignored; the fact that neurodegenerative pathologies can be seen together and potentiate the process were ignored. The second limitation is that descriptive statistics were presented as a number. In addition, the methodology of each study included in the review is different and the reviewed cases have a heterogeneous population. Moreover, the number of cases treated with exenatide or liraglutide in the reviewed studies was very small.

Conclusion

Many studies have reported that GLP-1 analog drugs significantly treat cognitive function losses, olfactory abnormalities, and cognitive disorders, especially in obese subjects. Some studies have, however, suggested that liraglutide administration cannot improve cognitive disorders in study group subjects compared to placebo group subjects. Although the exact effect of exenatide application in T2DM patients with neurodegenerative diseases is not known, liraglutide may be neuroprotective in individuals at risk of AD. Further multicenter, randomized clinical trials involving a large number of patients who are of different races are needed to insight into the effects of these drugs.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethic Permission

This study is a systematic review that does not involve human participation. Informed consent and ethical approval were not required.

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Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Code Availability

Not applicable.

Author Contributions

All authors contributed to the review. IY had the idea for the article, IY, BEB, BB, NK, NeK, and HO performed the literature search and data analysis, and all authors drafted and/or critically revised the review. All authors read and approved the fnal manuscript.

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