

REGISTERED REPORT PROTOCOL

GLP-1 and GIP receptor agonists in the treatment of Parkinson's disease: Translational systematic review and meta-analysis protocol of clinical and preclinical studies

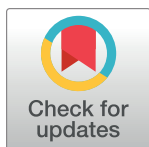
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Data Availability Statement: Since this is a study protocol, there is no pilot data yet. All relevant data from this study will be made available upon study completion.

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Abstract

Background

Parkinson's disease (PD) is a progressive multifactorial neurodegenerative condition. Epidemiological studies have shown that patients with type 2 diabetes mellitus (T2DM2) are at increased risk for developing PD, indicating a possible insulin-modulating role in this latter condition. We hypothesized that drugs similar to glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), used in the treatment of T2DM2, may play a role in PD.

Objectives

The purpose of this study is to systematically review and meta-analyze data of preclinical and clinical studies evaluating the efficacy and safety of GLP-1 and GIP drugs in the treatment of PD.

Methods

Two reviewers will independently evaluate the studies available in the Ovid Medline, Ovid Embase, Web of Science, Cochrane Central Register of Controlled Trials, Cinahl, and Lilacs databases. Preclinical rodent or non-human primate studies and randomized controlled human clinical trials will be included, without language or publication period restrictions. Outcomes of interest in preclinical studies will be primarily locomotor improvements and adverse effects in animal models of PD. For clinical trials, we will evaluate clinical improvements rated by the Movement Disorders Society Unified Parkinson's Disease Rating Scale—parts I, II, III, and IV, and adverse effects. The risk of bias of preclinical studies will be

Competing interests: The authors have declared that no competing interests exist.

assessed by the SYRCLE tool and CAMARADES checklist and the clinical studies by the Cochrane tool; the certainty of the evidence will be rated by GRADE.

Discussion and conclusion

There is an urge for new PD treatments that may slow the progression of the disease rather than just restoring dopamine levels. This study will comprehensively review and update the state of the art of what is known about incretin hormones and PD and highlight the strengths and limitations of translating preclinical data to the clinic whenever possible.

Systematic review registration

PROSPERO registration number [CRD42020223435](https://doi.org/10.1186/1745-6215-42020223435).

Background

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted by specific intestinal enteroendocrine cells in response to nutrient ingestion and absorption, preferably of carbohydrate and fat [1–3].

Both hormone effects are characterized by stimulation of pancreatic islet β cell proliferation and differentiation, as well as induction of glucose-dependent pancreatic insulin secretion [2, 4]. Curiously, GLP-1 also acts as a potent glucagon inhibitor in a postprandial state, while GIP stimulates glucagon release during fasting [2, 5, 6]. Together, they play an important role in regulating glycemic homeostasis, and, for that reason, analogs have been used in the treatment of type II diabetes mellitus (T2DM) [7, 8].

In addition to their conventional application in the T2DM treatment, several *in vitro* and *in vivo* studies [9–14] have evaluated the GLP-1 and GIP pleiotropic actions in extrapancreatic tissues, such as neuroprotective and neurotrophic effects in Parkinson's disease (PD) models.

PD is a chronic and progressive neurodegenerative disorder characterized by both motor and non-motor symptoms [15]. The pathological selective degeneration of dopaminergic neurons in one of the basal ganglia termed *substantia nigra pars compacta* (SNpc) culminates with reduced dopamine production and motor impairment. One of the morphological hallmarks of PD is the intracytoplasmic fibrillar aggregates referred to as Lewy bodies, in which the protein α -synuclein is a major component [15]. The causes of PD are not well defined. However, it is suggested that its pathogenesis is multifactorial, involving genetic susceptibility, aging and exposure to certain chemical agents [16].

T2DM has been associated with more severe symptoms and accelerated progression of PD [17–19]. The importance of metabolic dysfunction in PD is becoming widely accepted, including dysfunction of insulin signaling pathways [17, 20, 21].

In the CNS, insulin is behind many processes that could be dysregulated in PD, including apoptosis, autophagy, mitochondrial dysfunction, oxidative stress, neuroinflammation, and synaptic plasticity [22–27]. It is even possible that there is a relationship between the accumulation of the anomalous α -synuclein protein and the development of insulin resistance [22]. In transgenic mice with overexpression of alpha-synuclein, the accumulation of this protein appears to act as a negative regulator of the insulin signaling pathway by destabilizing its receptor substrate (Insulin receptor substrate-1, IRS-1) and inhibiting activation of the other important protein kinases of the pathway [28]. This may trigger a vicious cycle of

neuroinflammation and worsen the α -synuclein accumulation, which could lead to more neuronal loss.

Animal studies have shown that obese rats [29] or mice [30] or transgenic mice [31] with a diabetic profile are more susceptible to the neurotoxins used in PD animal models, such as by the development of brain insulin resistance [29, 31], accumulation of intracytoplasmic α -synuclein protein in the SNpc [31], activation of microglia cells (neuroinflammation) [31], endoplasmic reticulum stress in the midbrain [31], dopamine depletion in the SNpc and striatum [29], oxidative stress in dopaminergic neurons [29, 30] and/or dopaminergic neuronal loss [31].

Apart from peripheral tissues, the incretin hormone receptors are also expressed in the CNS [32–35]. The binding to GLP-1 and GIP receptors by GLP-1 and GIP agonists may restore brain insulin sensitivity by activation of specific insulin-modulated pathways that promote cell survival, while inhibiting pro-apoptotic pathways [36–39]. Therefore, interventions aimed at reversing insulin resistance are being increasingly recognized as possible new therapies for PD.

However, the GLP-1 and GIP receptor agonists may differ in their neuroprotective effects in view of pharmacodynamic and pharmacokinetic differences, and it is not quite clear if they would act as adjuvants in the treatment of PD with other usual antiparkinsonian drugs, or if they really could alter the progression of the disease.

Studies comparing different animal models of PD and different experimental designs with incretin hormones are scarce [40]. Either, there are a few randomized controlled trials with these analogs available in the literature; therefore, the possibility of translating the efficacy of this group of drugs from preclinical studies to the clinic has not yet been evaluated.

Translating the knowledge of basic research into new therapeutic approaches following the concept of "bench to bedside" is just one of the stages of translational medical research [41, 42]. Therefore, we propose to perform a systematic review and meta-analysis of randomized controlled clinical trials and preclinical studies evaluating the efficacy and safety of GLP-1 and GIP receptor agonists in slowing the progression of PD, exploring their potential mechanisms of neuroprotection. By analyzing preclinical and clinical studies, the ultimate goal is to verify if the results from preclinical studies can be translated into clinical practice whenever possible.

Methods

Standards

This protocol will follow established guidelines for systematic reviews and meta-analyses of clinical trials (PRISMA-P) [43], and specific guidelines for conducting systematic reviews of preclinical studies [44].

Protocol registration number

This protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42020223435).

Eligibility criteria

For clinical studies. *Study design.* Randomized controlled trials.

Participants. Studies including adults (≥ 18 years old) with a specialist-confirmed PD diagnosis (ICD-10: G20) according to the International Parkinson and Movement Disorder Society (MDS) criteria or the UK Parkinson's Disease Society Brain Bank diagnostic criteria, or on

the basis of clinical neurological assessment [45]. There will be no restrictions regarding sex, ethnicity or severity of PD.

Intervention. Studies including patients on treatment of PD with drugs capable of activating the following receptors:

- GLP-1: GLP-1, liraglutide, lixisenatide, semaglutide, geniposide, exenatide, exendin-4, oxytomodulin or others;
- GIP: D-Ala2-GIP-glu-PAL or others;
- GLP-1/GIP (dual agonists): DA-JC1, DA-JC4, DA-CH5, DA3-CH or others.

There will be no restrictions regarding duration and doses. Patients concomitantly receiving usual antiparkinsonian drugs (e.g., levodopa or dopaminergic drugs, such as monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors or dopaminergic agonists) will be accepted.

Comparators. Studies including specialist-confirmed PD patients who have not received treatment with GLP-1, GIP or dual GLP-1/GIP receptor agonist drugs. Participants on GLP-1/GIP placebos receiving standard of care (e.g., background treatment with antiparkinsonian drugs) will also be accepted.

Primary outcomes. Studies that measured:

- PD motor signs rated by the “Movement Disorders Society Unified Parkinson’s Disease Rating Scale—part III [46]”. A difference of -3.25 points will be considered a minimal, but clinically important, improvement and 4.63 points will be considered minimal, but clinically important, worsening [47].
- Non-motor symptoms rated by the MDS-UPDRS Scale, part I [46] or the Non-Motor Symptoms Questionnaire [48];
- Activities of daily living rated by the MDS-UPDRS Scale, part II [46];
- Dyskinesias or motor fluctuations rated by the MDS-UPDRS Scale part IV [46] or the Unified Dyskinesia Rating Scale [49];
- Adverse effects or serious adverse effects as reported in the included studies.

Secondary outcomes. Studies that measured:

- Quality of life rated by validated scales or questionnaires, such as the Parkinson’s Disease 39 item Quality of life questionnaire [50], the Parkinson’s disease quality of life questionnaire [51] or others;
- Psychological alterations, such as depression or dementia rated by the Mattis Dementia Rating Scale [52] or the Montgomery-Asberg Depression Rating Scale [53].

Exclusion criteria. Considering the potential association between diabetes and PD, we will exclude studies that exclusively enrolled patients with diabetes (any type). Furthermore, we will exclude studies involving participants with advanced dementia because cognitive impairment could affect the accuracy of patient-reported outcomes.

For preclinical studies. *Study design.* Any non-human studies using the following most common neurotoxin-induced animal models of PD for the establishment of therapeutic measures:

- 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, lipopolysaccharide, rotenone (or other possible pesticide exposure);

- Transgenic animal models that explore the function of PD-linked genes (e.g. α -synuclein, DJ-1, LRRK2, Parkin, UCH-L1, PINK1);
- Other models mentioned in the screened studies.

Animal species. Studies with adult rodents or non-human primates, without restriction as to strain, sex, life stage of exposure and/or moment of outcome evaluation.

Intervention. Studies including PD treatment with drugs capable of activating the following receptors:

- GLP-1: GLP-1, liraglutide, lixisenatide, semaglutide, geniposide, exenatide, exendin-4, oxytomodulin or others;
- GIP: D-Ala2-GIP-glu-PAL or others;
- GLP-1/GIP (dual agonists): DA-JC1, DA-JC4, DA-CH5, DA3-CH or others receptor agonist drugs.

Only studies that performed exposure to each drug separately will be accepted. There will be no restriction on dose level, route of administration or duration of exposure. Animals concomitantly treated with usual antiparkinsonian drugs will be accepted.

Comparators. Studies including PD or vehicle animals not exposed to the GLP-1, GIP or GLP-1/GIP receptor agonist drugs. Control animals treated with usual antiparkinsonian drugs will be accepted.

Primary outcomes. Studies that measured:

- Motor signs (motor activity and sensorimotor reflex) in tests commonly used to assess neurological parameters in rodents/non-human primates;
- Mortality or adverse effects, such as body weight changes, organ weight changes, macroscopical and histopathological analysis, liver or pancreatic enzyme levels, glucose levels, or others as reported in the included studies.

Secondary outcomes. Studies that measured cognitive functions/neurological behaviors and/or morphological changes that could be indicative of the GLP-1/GIP mode of action, such as:

- Learning and memory in tests commonly used to assess neurological parameters in rodents/non-human primates;
- Anxiety or depression behaviors measured by tests commonly used to assess neurological parameters in rodents/non-human primates;
- Number of nigrostriatal dopaminergic neurons by positive immunostaining of the tyrosine hydroxylase enzyme of neurons in the SNpc and other CNS regions;
- Quantification of dopamine levels and its metabolites in the striated nucleus or other CNS regions;
- Quantification of antiapoptotic signaling molecules;
- Evaluation of neuroinflammation by quantifying inflammatory cytokines or transcription factors involved in inflammatory response;
- α -synuclein accumulation in the SNpc and other CNS regions.
- Quantification of reactive oxygen species in dopaminergic neurons, as well as quantification of markers for oxidative stress and antioxidant enzymes;

- Quantification of neurotrophic factors related to neuroplasticity mechanisms.

Search methods for primary studies

Electronic searches. Peer-reviewed original studies published in the following electronic databases will be searched: Ovid Medline, Ovid Embase, Web of Science, Cochrane Central Register of Controlled Trials, Cinahl, and Lilacs without language and year of publication restrictions. Clinicaltrials.gov will also be consulted especially concerning possible unpublished trials with available data. All electronic searches will be performed from database inception to December, 2021.

Search strategy. Key terms, MeSH terms and free terms related to “Parkinson’s Disease”, “Parkinsonian Disorders”, “Glucagon-Like Peptide 1”, “Glucagon-Like Peptide 1 receptor”, “Exenatide”, “Liraglutide”, “Lixisenatide”, “Semaglutide”, “Geniposide”, “Oxytomodulin”, “D-Ala2-GIP-glu-PAL”, “DA-JC1”, “DA-JC4”, “DA-CH5”, “DA3-CH”, and “Glucose-dependent insulinotropic polypeptide” will be combined for each database (see [S1 Appendix](#) for an example of search strategy that will be adapted for each database).

Searching other resources. References listed in the selected studies will be analyzed for additional citations. Corresponding authors will be contacted to retrieve additional data.

Eligibility determination

Two reviewers (CV and DG), after calibration exercises, will independently screen all titles and abstracts identified by the literature search, obtain full-text articles of all potentially eligible studies, and evaluate them for eligibility. Disagreements will be resolved by consensus and, eventually, through consultation with technical advisors (JLVC, LCL, TVP) to improve accuracy and consistency among screeners.

Study flow diagram

A PRISMA flow diagram will be performed to indicate the number of included and excluded studies and the corresponding reasons for exclusion.

Data extraction

Reviewers (CV and DG) will undergo calibration exercises, and work in pairs to independently extract data from the included studies. A standardized, piloted form will be used to extract information from the clinical studies: reference, name of the evaluated drug, study design, severity of PD, name of the antiparkinsonian drugs possibly used concomitantly with the incretin analogs, treatment characteristics (dose, period of application, interval between applications, number of applications) and presentation of results (outcomes and the respective evaluation methods in the control and treatment groups).

For preclinical studies, the following information will be extracted: reference, name of the evaluated drug, description of the PD animal model (including strain, age, sex, the weight of animals and name of the PD-inducing neurotoxin or transgenic model), type and source of food used, conditions of the housing, control of temperature and humidity, characteristics of the test substance, experimental design (number of animals/group, acute or chronic exposure), treatment (doses, number of applications, vehicle, route of administration), euthanasia protocol, anesthetics possibly used, results (outcomes and the respective evaluation methods for control and treatment groups), and description of the statistics used. Whenever results in the preclinical studies are presented in graphs, the measures will be estimated by the Digitzeit software (version 2.4) in pairs, independently (CV and DG), and the mean of both measures will

be extracted in case of minor divergence. Disagreements will be resolved by consensus and, eventually, through consultation with technical advisors (JLVC, LCL, TVP) to improve accuracy and consistency among screeners.

Assessment of internal validity of individual studies

Two reviewers (CV and DG) will independently assess the internal validity of each study. Disagreements will be resolved by consensus and, eventually, through consultation with technical advisors.

For clinical studies, the Cochrane risk of bias tool will be used to assess the risk of bias [54, 55]. The following domains will be considered: a) selection bias (random sequence generation/allocation concealment); b) performance bias (blinding of participants and personnel); c) detection bias (blinding of outcome assessment); d) attrition bias (incomplete outcome data); e) other sources of bias.

For preclinical studies, specific assessment tools will be applied to evaluate the risk of bias, including the SYRCLE risk of bias tool [56] and the CAMARADES checklist [57], respectively.

The following domains will be considered for the risk of bias assessment: a) selection bias (random sequence generation/baseline characteristics/allocation concealment); b) performance bias (random housing/blinding of researchers during intervention); c) detection bias (random outcome assessment/outcome assessment blinding); d) attrition bias (incomplete outcome data); e) other sources of bias.

The possible answers for each domain in the risk of bias assessment of clinical and preclinical studies will be “Yes” (high risk of bias), “No” (low risk of bias) or “Unclear” (unclear risk of bias). Results will be presented in the form of tables and graphs.

Data synthesis and statistical analysis

Meta-analyses will be performed separately for preclinical and clinical studies, for each outcome (primary and secondary outcomes) through an inverse-variance random effects model. We will use the restricted maximum-likelihood (REML) estimator of the between-study variance. However, we will also present the results for the inverse-variance fixed-effects model as a sensitivity analysis.

Whenever feasible, inter-species comparison analyses will be performed to contrast the treatment effects observed in animal studies to those detected in human trials (e.g., a drug's effect on motor function in animals will be compared to the corresponding effects on humans). Inter-species comparisons will consider the direction, magnitude, and uncertainty of effects. Morphological outcomes in preclinical studies will be used to elucidate the GLP-1/GIP possible neuroprotective mode of action and will be in separate meta-analyses whenever possible or summarized in descriptive tables. All meta-analyses will be performed by the Stata software package (version 14.2) and presented in forest plots.

To perform the meta-analyses, the same measure of association will be calculated for the studies, depending on the type of data:

- Dichotomous outcome—Relative risks will be used as the effect measure, with a 95% confidence interval.
- Continuous outcome—Mean differences (MD) or standardized mean differences (SMD) will be used as the measure of treatment effect, with a 95% confidence interval.

Funnel plot asymmetry. Funnel plot asymmetry will be limited to outcomes with 10 or more estimates. We will plot a measure of precision (e.g., standard error) on the vertical axis

and the corresponding estimate on the horizontal axis. We will also use Egger's regression test for continuous outcomes and Harbord's test for binary outcomes [58, 59].

Heterogeneity assessment. Heterogeneity among individual studies will be assessed using the I^2 statistic and Cochran's Q test [60]. The latter will be considered statistically significant when $P < 0.10$.

Meta-regression and subgroup analysis. Meta-regression models with the REML estimator of the between-study variance will be fitted whenever 10 or more estimates are available. If less than 10 estimates are available, subgroup analyses will be performed. Meta-regression and subgroup analyses will be conducted whenever possible (at least 2 studies) to investigate possible sources of heterogeneity in clinical studies, such as due to the inclusion of participants with different PD severity (severe, moderate and mild scored on the MDS-UPDRS part III), subtypes of PD (tremor dominant, mixed and akinetic/rigid), genomic status of each patient's PD related genes (α -synuclein, DJ-1, LRRK2, Parkin, UCH-L1 or PINK1), use of other antiparkinsonian drugs (levodopa or dopaminergic drugs, such as monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors or dopaminergic agonists), and different treatment schemes with the GLP-1, GIP or GLP-1/GIP receptor agonists (different doses, route of administration and duration of treatment). In case of concomitant use with other antiparkinsonian drugs, we will consider whether the patients were in an "off" medication state (with the withdrawal of the medication at least the day before the evaluations). Whenever possible, "on" and "off" state measures will be compared separately since it is expected a higher magnitude of effect in an "on" medication state.

For preclinical studies, heterogeneity will be investigated considering the use of different animal species (rats, mice and non-human primates), different PD models (different neurotoxins and transgenic models), different PD severity (partial and full lesions), use of other antiparkinsonian drugs (levodopa or dopaminergic drugs, such as monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors or dopaminergic agonists) and different treatment schemes (different doses, route of administration and duration of treatment).

If there are enough studies (at least 2), we will investigate the impact of high risk of bias studies on the meta-analyses in a sensitivity analysis.

If it is not possible to pool results in the meta-analyses due to high not explained heterogeneity or not enough similar data for each outcome, findings will only be narratively described.

Certainty of evidence

The GRADE system [61–63] will be used to rate the certainty of evidence provided by preclinical and clinical studies separately. The certainty of evidence will be determined for each outcome. Randomized controlled clinical trials and animal studies, when well designed, can eliminate much of the confounding factors by random allocation of participants and animals to the different study groups. Thus, they start from the initial classification of "high certainty".

However, there are several factors that can downgrade the initial classification of the study groups in relation to the reliability of the evidence that they generated: risk of bias [64], imprecision [65], inconsistency [66], indirectness [67], and publication bias [68].

Four descriptors will be used to indicate the level of confidence in the evidence generated by preclinical and clinical studies, separately: high certainty level (++++); moderate certainty level (+++); low certainty level (++); very low certainty level (+). All results will be presented as tables.

Highly reliable evidence implies that further studies will hardly change the available results; on the other hand, very low levels of evidence indicate that future studies may alter not only the confidence in the available results, but the results themselves.

Discussion and conclusion

Ever since its discovery in the late 60s, levodopa remains the gold standard for the symptomatic treatment of PD [69]. Levodopa is a dopamine precursor that easily crosses the blood-brain barrier, and in the CNS is converted to dopamine to restore the low dopamine levels caused by dopaminergic neuron degeneration. However, long-term levodopa treatment is frequently associated with motor fluctuations and dyskinesias that have a serious impact on patient quality of life [69].

Currently, the goal for the treatment of PD is the development of drugs that may slow the progression of the disease, instead of just restoring dopamine levels. GLP-1 and GIP receptor agonists have been indicated as possible neuroprotectors due to a reduction in neuronal insulin resistance in a variety of preclinical models [22, 36–38].

The use of animal models has been crucial to elucidate the pathophysiology behind PD and the development of therapeutic strategies. However, each model has its own particularities and there is still no single model that mimics all the human features of PD [70, 71].

Although the clinical aspects in animals are not the same as in humans, there are different locomotor tests that investigate bradykinesia, decreased motor activity, tremors, muscle rigidity or motor coordination in animals, besides neurobehavioral conditions, such as anxiety, depression, memory loss and others [71]. In the present work, corresponding outcomes will be used for more straightforward comparisons with clinical findings in humans whenever possible. The morphological outcomes in animals will be used to investigate the mechanisms of action in both animals and humans. Naturally, the future discussion will also take into account the applicability and limitations of the current PD animal models.

It is acknowledged that, as each outcome will be evaluated separately, meta-analyses and subgroup analyses eventually will not be possible due to the lack of studies with similar data or due to high heterogeneous findings. It is also possible to predict a low number of clinical trials that do not address all drugs identified in preclinical studies.

Nevertheless, this study will update the state of the art in terms of what is known about incretin hormones and PD and provide a critical appraisal on the possible efficacy and safety of these drugs in altering the course of the disease, highlighting the strengths and limitations of translating preclinical data to the clinic whenever possible.

Supporting information

S1 Checklist. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: Recommended items to address in a systematic review protocol*.

(DOC)

S1 Appendix. Search strategy OVID MEDLINE. Search strategy example to be adapted for each database.

(DOCX)

Author Contributions

Conceptualization: Carolina Vaccari, Denise Grotto, Tiago da V. Pereira, João Lauro V. de Camargo, Luciane C. Lopes.

Methodology: Carolina Vaccari, Denise Grotto, Tiago da V. Pereira, João Lauro V. de Camargo, Luciane C. Lopes.

Supervision: João Lauro V. de Camargo, Luciane C. Lopes.

Writing – original draft: Carolina Vaccari.

Writing – review & editing: Carolina Vaccari, Denise Grotto, Tiago da V. Pereira, João Lauro V. de Camargo, Luciane C. Lopes.

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