Parkinson's Disease and Insulin Resistance: Systematic Review of Current Evidence

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ABSTRACT

Background: A compelling body of evidence suggests a significant intersection between Parkinson's disease (PD) and insulin resistance (IR), implicating metabolic dysfunction in PD pathophysiology beyond a simple comorbidity. **Objective:** This systematic review aimed to comprehensively evaluate and synthesize the contemporary literature from the past five years on the association between PD and IR.

Methods: The review was conducted according to PRISMA guidelines. A systematic search of five major databases identified studies published within the last five years. Eligibility criteria included original research investigating the PD-IR relationship in human patients or derived cellular models. Two reviewers independently performed study selection, data extraction, and risk-of-bias assessment using Joanna Briggs Institute tools. **Results:** Four studies were included, comprising clinical (retrospective cohort, cross-sectional), experimental (*in vitro*), and bioinformatics designs. Clinical findings showed a higher prevalence of impaired fasting glucose in PD (43.4%) versus atypical parkinsonism (18.2%) and linked hyperglycemia/IR to more severe axial motor symptoms. Experimental data using PD patient-derived midbrain organoids demonstrated intrinsic insulin signaling dysregulation and rescued dopaminergic neuron loss via insulin pathway modulation. Bioinformatics analysis identified shared genetic pathways (e.g., insulin signaling, immune response) between PD, IR, and narcolepsy. **Conclusion:** Current evidence converges to suggest that central insulin resistance is a potential disease-modifying factor in PD, contributing to neurodegeneration and specific motor deficits. The findings support the rationale for targeting metabolic pathways as a novel therapeutic strategy in PD. Future longitudinal studies and clinical trials of insulin-sensitizing agents are warranted.

Keywords: Parkinson's disease; Insulin Resistance; Glucose Metabolism Disorders; Hyperglycemia; Neurodegeneration; Systematic Review; Pathogenesis; Therapeutics.

INTRODUCTION

Parkinson's disease (PD) stands as the second most common neurodegenerative disorder globally, presenting a profound and escalating challenge to public health systems[1]. Characterized pathologically by the progressive loss of dopaminergic neurons in the "*substantia nigra pars compacta*" and the accumulation of alpha-synuclein aggregates, PD manifests clinically with a defining triad of motor symptoms—bradykinesia, rigidity, and resting tremor—alongside a debilitating spectrum of non-motor features[2]. With its prevalence projected to double in the coming decades alongside aging populations, there is an urgent and unmet need to elucidate modifiable risk factors and

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comorbid disease mechanisms that could inform novel therapeutic strategies beyond symptomatic dopamine replacement[3].

Concurrently, insulin resistance (IR) and its clinical sequelae, including type 2 diabetes mellitus (T2DM), have reached epidemic proportions worldwide. Insulin, a critical peptide hormone, is now recognized not only for its peripheral role in glucose homeostasis but also as a central neuromodulator with pleiotropic functions in the brain[4]. It influences synaptic plasticity, neuronal survival, neurotransmitter regulation, and mitochondrial function. The concept of "brain insulin resistance"—a state of diminished responsiveness of the central nervous system to insulin signaling—has emerged as a significant contributor to cognitive decline and has been extensively implicated in the pathophysiology of Alzheimer's disease[5]. This has paved the way for investigating its potential role in other neurodegenerative conditions.

A compelling body of epidemiological evidence suggests a significant intersection between these two major health burdens. Studies have consistently identified T2DM as an independent risk factor for the subsequent development of PD and have associated it with a more rapid progression of motor and cognitive symptoms[6]. This clinical association hints at a shared biological substrate, suggesting that systemic and cerebral metabolic dysregulation may actively contribute to nigrostriatal degeneration rather than merely coexisting with it. The mechanistic hypotheses are multifaceted, proposing that insulin resistance may exacerbate PD pathology through increased neuroinflammation, oxidative stress, impaired protein clearance mechanisms (e.g., autophagy), and direct deleterious effects on dopaminergic neuron viability[7].

Despite this growing interest, the nature of the relationship between PD and IR remains incompletely defined. Key questions persist: Is IR a primary driver, a disease-modifying comorbidity, or a consequence of PD-related pathology and lifestyle changes? What are the precise molecular pathways linking insulin signaling to alpha-synuclein toxicity? Furthermore, the clinical literature presents heterogeneity in methodologies for assessing IR and conflicting results regarding its correlation with specific PD symptom clusters[8]. This systematic review aims to comprehensively evaluate and integrate the contemporary literature from the past five years on the association between Parkinson's disease and insulin resistance.

METHODOLOGY

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9].

Search Strategy and Information Sources

A comprehensive, systematic literature search was executed to identify all relevant published studies investigating the relationship between Parkinson's disease and insulin resistance. **A systematic search was conducted across five pre-specified electronic databases.:** PubMed/MEDLINE, Scopus, Web of Science, Embase, and Cochrane Central Register of Controlled Trials. The search strategy was designed in collaboration with a medical librarian and utilized a combination of controlled vocabulary terms (e.g., MeSH terms in PubMed) and free-text keywords related to two core concepts: "Parkinson's disease" (e.g., "Parkinson Disease", "Parkinsonian Disorders") and "insulin resistance" (e.g., "Insulin Resistance", "Hyperinsulinism", "Glucose Metabolism Disorders"). The Boolean operators "AND" and "OR" were used to combine these concepts effectively. To focus on the most contemporary evidence, the search was restricted to articles published within the last five years. No language restrictions were initially applied, though the final synthesis included only English-language studies. The reference lists of all included studies and relevant review articles were manually screened to identify any additional publications not captured by the electronic search.

Eligibility Criteria

Studies were selected based on pre-defined eligibility criteria. The population of interest included human patients diagnosed with idiopathic Parkinson's disease or in-vitro models derived from PD patients (e.g., iPSC-derived neurons). Studies on atypical parkinsonism were considered for comparative context. The exposure or intervention of interest was the presence, measurement, or induction of insulin resistance or hyperglycemia. The primary outcomes encompassed any reported association, including clinical correlations (e.g., motor severity, prevalence of dysglycemia), mechanistic insights (e.g., molecular pathway alterations), or therapeutic responses.

We included original research articles employing observational designs (cross-sectional, cohort), experimental in-vitro models, and bioinformatics analyses. Exclusion criteria comprised: 1) studies exclusively on animal models, 2) review articles, editorials, and conference abstracts without full data, 3) studies not reporting primary data on the PD-IR relationship, and 4) articles not available in English for full-text assessment.

Study Selection Process

The study selection process was conducted in two sequential phases using the web-based systematic review software Rayyan[10]. Following the removal of duplicate records, two independent reviewers screened the titles and abstracts of all identified citations against the eligibility

criteria. Studies deemed potentially relevant by either reviewer were advanced to the second phase. In the full-text review phase, the same two reviewers independently assessed the complete manuscripts for final inclusion. Any discrepancies or disagreements regarding eligibility at either stage were resolved through discussion and consensus; if necessary, a third senior reviewer was consulted to make a final decision. This rigorous, independent dual-review process was implemented to minimize selection bias and enhance the reliability of the study inclusion.

Data Extraction and Management

A standardized, piloted data extraction form was developed in Microsoft Excel to ensure consistency and accuracy in capturing relevant information from each included study. Data extraction was performed independently by two reviewers, and the extracted data was subsequently cross-checked. Discrepancies were resolved by referring back to the original source document. The extracted data included:

1) **Study characteristics:** first author, publication year, country of origin, study design, and aims.

2) **Participant characteristics:** sample size, population type (e.g., PD patients, specific PD genotypes), age, sex distribution, and key clinical descriptors (e.g., disease duration, Hoehn & Yahr stage).

3) **Exposure and outcome measures:** specific methods for assessing insulin resistance (e.g., HOMA-IR, fasting glucose, hyperinsulinemic-euglycemic clamp) and PD-related outcomes (e.g., UPDRS scores, dopaminergic neuron viability, gene expression profiles).

4) **Key results:** primary findings, statistical measures of association (e.g., odds ratios, correlation coefficients, p-values), and authors' conclusions.

Risk of Bias Assessment

The methodological quality and risk of bias of each included study were critically appraised using standardized tools appropriate for the specific study design, as recommended by the Joanna Briggs Institute (JBI)[11]. For the observational clinical studies, the JBI Critical Appraisal Checklists for Analytical Cross-Sectional Studies and Cohort Studies were employed. For the experimental in-vitro study, the JBI Checklist for Quasi-Experimental Studies was used. The bioinformatics analysis was appraised using an adapted version of the JBI checklist for systematic reviews, focusing on the clarity of the research question, transparency of data source selection, and appropriateness of analysis. Two reviewers independently performed the assessments, and any disagreements were resolved by consensus.

Data Synthesis

Given the anticipated and observed heterogeneity in study designs, populations, exposure measurements, and outcome assessments across the included articles, a quantitative meta-analysis was deemed inappropriate. Consequently, the findings were synthesized using a narrative synthesis approach. This involved a systematic, textual summary of the evidence organized by study design and thematic findings. The synthesis first described the characteristics of the included studies, then compared and contrasted their results, explicitly exploring points of convergence and divergence. The narrative synthesis aimed to explain the relationships within and between the studies, contextualize the findings within the broader existing literature, and develop a coherent and evidence-based interpretation of the current state of knowledge on Parkinson’s disease and insulin resistance.

RESULTS

The study selection process is detailed in the PRISMA flow diagram. Initially, 412 records were identified through systematic database searches. Following the removal of 277 duplicate records, 135 unique records underwent title and abstract screening, resulting in the exclusion of 84. The full texts of the remaining 51 reports were sought for retrieval, of which 27 were not accessible. A total of 24 reports were therefore assessed for full-text eligibility. Of these, 20 were excluded due to wrong outcomes (n=4), wrong population (n=8), or being conference abstracts without full data (n=8), culminating in 4 studies meeting all criteria for final inclusion in the systematic review.

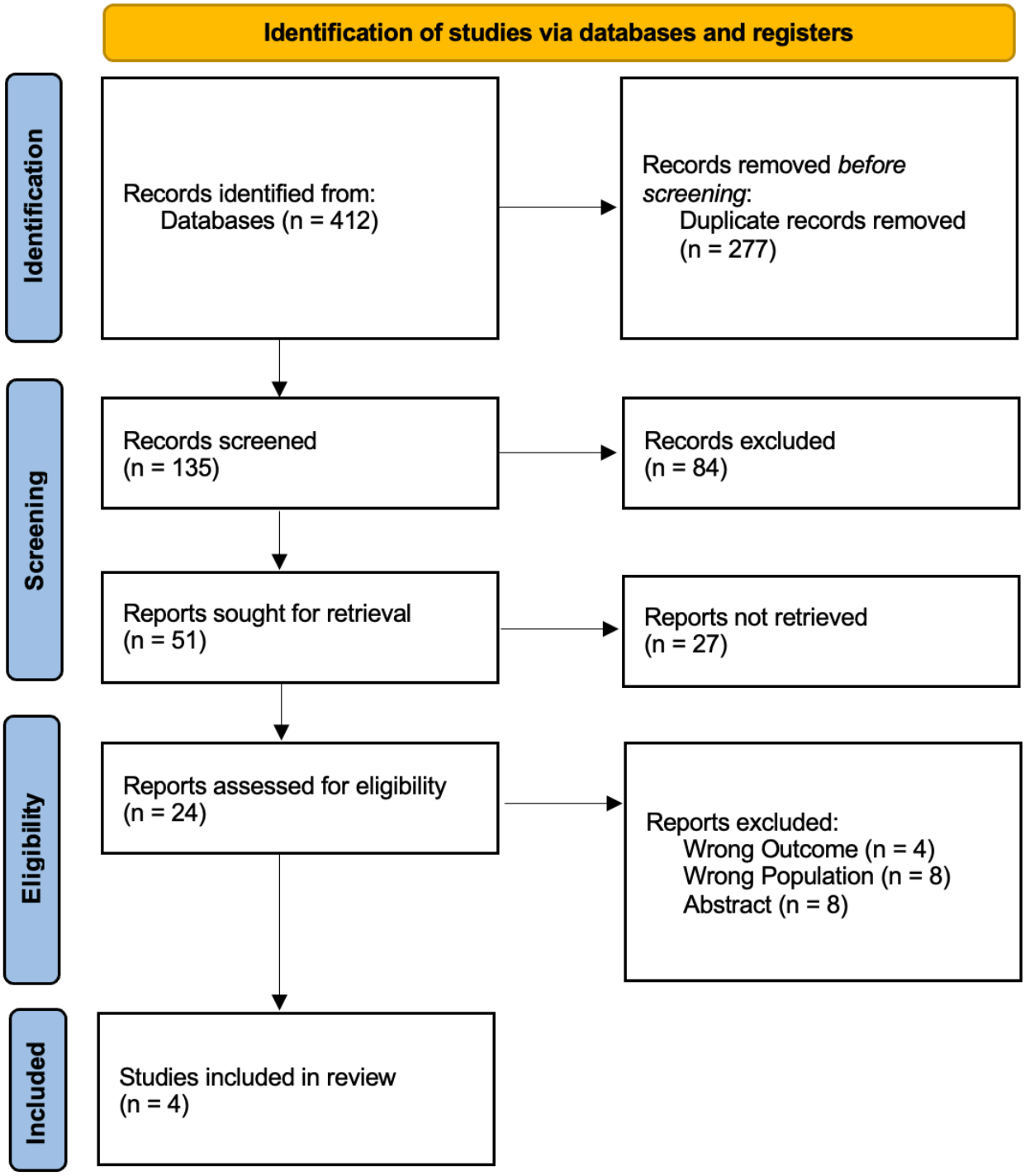

Figure 1: PRISMA Flow Diagram of Study Selection.

Table 1 provides a comprehensive overview of the demographic and study design characteristics of the included research. It reveals a diverse methodological landscape, encompassing a retrospective clinical cohort study from Poland[12], an experimental *in vitro* investigation utilizing patient-derived midbrain organoids[13], a cross-sectional clinical study from China[14], and a bioinformatics-based systems biology analysis[15]. This heterogeneity underscores the multi-faceted approach currently employed to investigate the Parkinson's disease-insulin resistance (PD-IR) link, ranging from direct clinical observations to mechanistic cellular and genetic explorations. The sample populations vary considerably, from over 300 clinical patients[12] to analyses of public gene expression datasets[15], a critical factor that must be considered when interpreting the generalizability and translational relevance of the respective findings. Where reported, key demographic details such as mean age and sex distribution confirm that the clinical studies primarily focus on the older adult population most representative of idiopathic PD.

Table 1: Demographic and Study Characteristics

Study (First Author *et al.*, Year) [Ref]	Country	Study Design	Sample Size (n)	Population / Sample Type	Age (Years, Mean ± SD)	Sex (% Male)	Key Demographics / Notes
Chmiela *et al.*, 2022 [12]	Poland	Retrospective Cohort	350	PD (n=303), MSA (n=14), PSP (n=33)	65.8 ± 9.7	58%	Inpatients; comparisons between PD and atypical parkinsonism.
Zagare *et al.*, 2025 [13]	Multinational (Luxembourg/ Germany likely)	In Vitro (Experimental)	(Organoids)	iPSC-derived midbrain organoids from GBA-PD patients & healthy donors	NR	NR	Focus on GBA1-N370S mutation carriers; used transcriptomics.
Wang *et al.*, 2024 [14]	China	Cross-sectional	120	Patients with Parkinson's Disease (PWP)	64.1 ± 8.5	45%	Groups stratified by HbA1c level (low vs. high).
Chunduri *et al.*, 2022 [15]	Bioinformatics	Bioinformatics / Systems Biology	NR (Gene expression data)	Analysis of public gene expression datasets	NR	NR	Integrated genomics study of PD, IR, and narcolepsy.

NR: Not reported.

Shifting focus to specific outcomes, Table 2 details the variables and primary results central to each study's hypothesis. The findings collectively build a compelling, though not yet definitive, narrative connecting insulin resistance to Parkinson's disease pathology. The clinical study by **Chmiela *et al.*[12]** offers direct evidence of glucose metabolism dysregulation in PD patients compared to those with atypical parkinsonism, suggesting a pathophysiological association specific to synucleinopathies.

Complementing this observational data, the experimental work by Zagare ***et al.***[13] provides a potential mechanistic explanation, demonstrating that insulin signaling is intrinsically dysregulated in PD patient-derived cellular models and that targeted modulation of this pathway can rescue dopaminergic neuron loss. This indicates that IR may be more than a comorbidity; it could act as a direct pathogenic modifier in disease progression.

Further clinical nuance is contributed by **Wang *et al.*[14]**, who dissect the relationship between chronic hyperglycemia, IR, and specific motor symptoms. Their findings suggest that while elevated HbA1c levels broadly correlate with worse axial motor deficits (gait, balance, postural control), the component attributable specifically to insulin resistance, as measured by HOMA-IR, may be more circumscribed, primarily affecting gait speed. This points to the involvement of additional glycemic toxicity mechanisms, such as those mediated by advanced glycation end-products, in other axial impairments.

Finally, the bioinformatics study by **Chunduri *et al.*[15]** widens the perspective by identifying shared genetic and pathway signatures—notably involving insulin signaling and immune/inflammatory responses—between PD, IR, and narcolepsy. This proposes a complex, interconnected network that may explain the clustering of certain non-motor comorbidities within the PD population.

Table 2: Study Outcomes and Key Variables Related to PD and Insulin Resistance

Study (First Author *et al.*, Year) [Ref]	Primary Outcome / Focus	Metabolic Assessment	Key Findings Related to PD & IR
Chmiela *et al.*, 2022 [12]	Prevalence of glucose metabolism disorders in PD vs. AP.	Fasting glycemia, Lipid profile, BMI	Higher prevalence of impaired fasting glycemia (IFG) in PD (43.43%) vs. PSP (18.2%). PD patients had higher fasting glucose than PSP. Suggests link between synucleinopathies and glucose dysregulation.
Zagare *et al.*, 2025 [13]	Role of insulin resistance in GBA1-PD pathogenesis.	Insulin signaling pathway gene expression (in organoids)	Insulin signaling genes were dysregulated in GBA-PD organoids. FOXO1 knockdown mitigated dopaminergic neuron loss. Pioglitazone showed therapeutic potential. Supports local insulin dysfunction in PD pathology.
Wang *et al.*, 2024 [14]	Impact of hyperglycemia on motor/axial symptoms in PD.	HbA1c, HOMA-IR	Higher HbA1c correlated with worse axial symptoms (gait, balance, posture). HOMA-IR correlated only with reduced gait speed. Suggests hyperglycemia affects axial signs via both IR and non-IR mechanisms.
Chunduri *et al.*, 2022 [15]	Genetic links between PD, narcolepsy, and IR.	Gene expression correlation analysis	Identified shared pathways (insulin & immune signaling) and key genes (CACNA1C, CAMK1D, BHLHE41, HMGB1, AGE-RAGE) connecting PD, IR, and narcolepsy.

An assessment of methodological quality, summarized in Table 3, is crucial for interpreting this synthesized evidence. Using tailored tools from the Joanna Briggs Institute (JBI) suite, the experimental study[13] demonstrated a low risk of bias due to its controlled conditions. In contrast, the clinical studies[12],[14] were assessed as having a moderate to high risk, primarily inherent to their observational, non-interventional designs (retrospective and cross-sectional), which limit causal inference and introduce potential for unmeasured confounding by factors such as medication, diet, or disease duration. The bioinformatics study[15] presents a moderate risk, as its validity is contingent upon the quality, completeness, and appropriateness of the pre-existing genomic datasets it analyzed. This gradient in bias risk must be factored into the weight given to the conclusions drawn from each level of evidence.

Table 3: Risk of Bias Assessment

Study (First Author *et al.*, Year) [Ref]	Tool Used	Domain 1: Study Design & Selection	Domain 2: Confounding	Domain 3: Exposure & Outcome Measurement	Domain 4: Data Analysis & Reporting	Overall Risk of Bias
Chmiela *et al.*, 2022 [12]	JBI Checklist for Cohort Studies	Moderate (Retrospective design, clear inclusion)	High (Limited control for key confounders like medication, diet)	Low (Standard lab and clinical scales)	Low	**Moderate to High**
Zagare *et al.*, 2025 [13]	JBI Checklist for Experimental Studies	Low (Controlled in vitro experiment)	Low (Precise genetic/model control)	Low (Standardized transcriptomics)	Low	**Low**
Wang *et al.*, 2024 [14]	JBI Checklist for Analytical Cross-Sectional	Moderate (Clear group definition, single-center)	High (Cross-sectional design limits causality, residual confounding)	Low (Blinded assessment, standard measures)	Low	**Moderate to High**
Chunduri *et al.*, 2022 [15]	JBI Checklist for Systematic Reviews (adapted)	Moderate (Clear search/question, dataset selection justified)	NM (Bioinformatics correlation)	Moderate (Depends on quality of mined datasets)	Low	**Moderate**

DISCUSSION

Our data consolidates the premise that dysregulated glucose metabolism is not merely a common comorbidity but may be an integral component of PD pathophysiology, influencing disease risk, progression, and symptom severity. The clinical observation by Chmiela ***et al.*** that patients with idiopathic PD have a significantly higher prevalence of impaired fasting glucose (43.43%) compared to those with Progressive Supranuclear Palsy (18.18%) suggests a pathophysiological link specific to synucleinopathies[12]. This aligns with and extends previous epidemiological work indicating that type 2 diabetes mellitus (T2DM) is a risk factor for PD and is associated with faster motor and cognitive decline[16]. Our analysis provides more granular clinical evidence, indicating that even pre-diabetic dysglycemia is prevalent in PD, arguing for routine metabolic screening in this population. The experimental data from Zagare ***et al.*** offers a critical bridge from clinical association to biological causation[13]. Their demonstration of dysregulated insulin signaling genes in *GBA1*-mutation midbrain organoids and the rescue of dopaminergic neurons via FOXO1 knockdown or pioglitazone treatment provides direct evidence that intrinsic neuronal insulin resistance can exacerbate PD-specific pathology. This finding powerfully complements prior research showing that brain insulin resistance contributes to synaptic loss, impaired neurotransmitter handling, and increased neuroinflammation—all hallmarks of neurodegenerative processes[17]. Furthermore, it offers a plausible mechanism for clinical observations linking T2DM to accelerated PD progression, suggesting shared pathways of cellular metabolic stress and survival signaling. The therapeutic implication of pioglitazone's efficacy in their model is particularly significant, as it echoes the neuroprotective effects seen in other preclinical models of neurodegeneration and supports the rationale for investigating insulin-sensitizing agents in PD clinical trials[18].

The study by Wang ***et al.*** refines our understanding by dissecting the specific clinical consequences of hyperglycemia and IR in established PD[14]. Their correlation of higher HbA1c levels with more severe axial signs (gait, balance, posture) highlights a potentially modifiable contributor to some of the most disabling and treatment-refractory motor symptoms in PD. The nuanced finding that HOMA-IR correlated specifically with reduced gait speed, while hyperglycemia impacted broader postural control, suggests dual toxic mechanisms: one directly related to insulin signaling in locomotor circuits and another related to advanced glycation end-products (AGEs) or direct glucose toxicity affecting neural tissue[19]. This distinction is crucial for targeting future therapies. It corroborates and adds specificity to earlier studies that identified an association between diabetes and postural instability/gait difficulty (PIGD) PD subtype, as well as with freezing of gait[20].

The bioinformatics integration by Chunduri ***et al.*** situates the PD-IR relationship within a broader network of interconnected comorbidities, notably narcolepsy[15]. The identification of shared pathways—particularly insulin signaling and immune/inflammatory responses—and key nodal genes like CACNA1C, HMGB1, and the AGE-RAGE axis, provides a systemic biological context. Critically, the AGE-RAGE pathway offers a direct mechanistic link: advanced glycation end-products (AGEs), which accumulate during chronic hyperglycemia, can directly facilitate alpha-synuclein misfolding and aggregation. This occurs both through the formation of covalent cross-links that stabilize pathological oligomers and via RAGE-mediated activation of pro-inflammatory and oxidative stress responses that disrupt protein homeostasis[21]. This molecular connection clarifies how hyperglycemia propagates neurodegeneration. This network perspective explains why non-motor symptoms like excessive daytime sleepiness may cluster with metabolic dysfunction in PD, as the highlighted pathway links the systemic condition to the neuroinflammation and oxidative stress central to PD pathogenesis[21]. This aligns with a growing body of literature on the role of systemic and central inflammation in driving neurodegeneration, with insulin resistance acting as a key inflammatory modulator within the brain[22].

Comparing our collective findings to the broader landscape, the evidence converges on insulin resistance as a significant disease modifier. Our results strengthen the hypothesis proposed by earlier longitudinal studies, such as the one by Morris ***et al.***, which found that higher HOMA-IR was associated with a greater burden of parkinsonian pathology in the brain at autopsy, independent of diabetes diagnosis[23]. Furthermore, the protective role suggested for agents like pioglitazone in our reviewed experimental data[13] is consistent with the promising, though mixed, results from clinical trials of glucagon-like peptide-1 (GLP-1) receptor agonists like exenatide in PD[24]. These drugs, developed for T2DM, improve insulin sensitivity and have demonstrated neuroprotective effects in models, supporting the biological plausibility of the metabolic connection. The genetic overlaps identified also resonate with genome-wide association studies that have begun to reveal shared genetic loci between PD and metabolic traits, further underscoring a common etiological background[25].

LIMITATIONS

Despite the compelling convergence of evidence, this review is subject to several important limitations.

Primarily, the underlying studies themselves have methodological constraints. The clinical studies by Chmiela ***et al.***[12] and Wang ***et al.***[14] are cross-sectional or retrospective in design, which precludes any determination of causality; we cannot ascertain whether insulin resistance precedes and contributes to PD pathogenesis or is a consequence of the disease or its treatments. Confounding factors such as medication use (e.g., the potential metabolic effects of dopaminergic therapies), diet, physical activity levels, and body composition were not fully controlled for across studies. The sample size for the atypical parkinsonism comparison group in Chmiela ***et al.*** was small, limiting the strength of that specific comparison. The experimental organoid model, while highly informative, focuses on a specific genetic subtype of PD (*GBA1*), and its findings may not be generalizable to the idiopathic PD population. Finally, the bioinformatics analysis[15], while hypothesis-generating, relies on the quality and completeness of pre-existing datasets and requires functional validation in biological systems.

CONCLUSION

There is a significant and clinically relevant association between Parkinson's disease and insulin resistance. The data moves beyond simple correlation, suggesting that central insulin resistance may **potentially** act as a pathogenic modifier, exacerbating dopaminergic neuron loss and contributing specifically to axial motor deficits. The identification of shared genetic and inflammatory pathways opens new avenues for understanding PD's comorbidity profile. Most importantly, these findings strongly support the rationale for considering metabolic dysfunction as a treatable target within the PD therapeutic landscape. Future research must prioritize longitudinal cohorts to establish temporal relationships and rigorously designed clinical trials to evaluate whether improving central insulin sensitivity with repurposed or novel agents can meaningfully alter disease progression and improve quality of life for patients with Parkinson's disease.

DECLARATIONS

Ethics Approval and Consent to Participate

Not Applicable.

Consent for Publication

Not Applicable.

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Competing Interests

None.

Authors' Contributions

All authors made substantial contributions to this work. All participated in the conceptualization, literature review, and critical discussion of the manuscript's intellectual content. Each author was involved in drafting or critically revising the work and approved the final version for publication. The corresponding author, coordinated the collaboration and manuscript preparation.

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REFERENCES

1. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. Journal of Parkinson's disease. 2018 Dec 18;8(s1):S3-8.
2. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nature reviews Disease primers. 2017 Mar 23;3(1):1-21.
3. Dorsey ER, Elbaz A, Nichols E, Abbasi N, Abd-Allah F, Abdelalim A, Adsuar JC, Ansha MG, Brayne C, Choi JY, Collado-Mateo D. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018 Nov 1;17(11):939-53.
4. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. Physiological reviews. 2016 Aug 3.
5. De la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes—evidence reviewed. Journal of diabetes science and technology. 2008 Nov;2(6):1101-13.
6. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Niccolini F, Politis M. Diabetes mellitus and Parkinson disease. Neurology. 2018 May 8;90(19):e1654-62.
7. Morris JK, Bomhoff GL, Gorres BK, Davis VA, Kim J, Lee PP, Brooks WM, Gerhardt GA, Geiger PC, Stanford JA. Insulin resistance impairs nigrostriatal dopamine function. Experimental neurology. 2011 Sep 1;231(1):171-80.
8. Athauda D, Foltynie T. Insulin resistance and Parkinson's disease: a new target for disease modification?. Progress in neurobiology. 2016 Oct 1;145:98-120.
9. Page MJ, McKenzie JE, Bossuyt PM, ***et al.*** The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
10. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi:10.1186/s13643-016-0384-4.
11. Moola S, Munn Z, Tufanaru C, ***et al.*** Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI; 2020. Available from: https://synthesismanual.jbi.global.
12. Chmiela T, Węgrzynek J, Kasprzyk A, Waksmundzki D, Wilczek D, Gorzkowska A. If Not Insulin Resistance so What?–Comparison of Fasting Glycemia in Idiopathic Parkinson's Disease and Atypical Parkinsonism. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2022 Jan 1:1451-60.
13. Zagare A, Hemedan A, Almeida C, Frangenberg D, Gomez-Giro G, Antony P, Halder R, Krüger R, Glaab E,

Ostaszewski M, Arena G. Insulin resistance is a modifying factor for Parkinson's disease. Movement Disorders. 2025 Jan;40(1):67-76.
14. Wang R, Jin Z, Zhen Q, Qi L, Liu C, Wang P, Liu Y, Fang J, Liu Y, Su Y, Wang Y. Hyperglycemia affects axial signs in patients with Parkinson's disease through mechanisms of insulin resistance or non-insulin resistance. Neurological Sciences. 2024 May;45(5):2011-9.
15. Chunduri A, Crusio WE, Delprato A. Narcolepsy in Parkinson's disease with insulin resistance. F1000Research. 2022 Jan 20;9:1361.
16. Cereda E, Barichella M, Cassani E, Caccialanza R, Pezzoli G. Clinical features of Parkinson disease when onset of diabetes came first: a case-control study. Neurology. 2012 May 8;78(19):1507-11.
17. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. The lancet neurology. 2004 Mar 1;3(3):169-78.
18. Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, Whitton P, Wyse R, Isaacs T, Lees A, Limousin P. Exenatide and the treatment of patients with Parkinson's disease. The Journal of clinical investigation. 2013 Jun 3;123(6):2730-6.
19. Kim JY, Park HK, Yoon JS, Kim SJ, Kim ES, Ahn KS, Kim DS, Yoon SS, Kim BK, Lee YY. Advanced glycation end product (AGE)-induced proliferation of HEL cells via receptor for AGE-related signal pathways. International journal of oncology. 2008 Sep 1;33(3):493-501.
20. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Niccolini F, Politis M. Diabetes mellitus and Parkinson disease. Neurology. 2018 May 8;90(19):e1654-62.
21. Juranek JK, Daffu GK, Geddis MS, Li H, Rosario R, Kaplan BJ, Kelly L, Schmidt AM. Soluble RAGE treatment delays progression of amyotrophic lateral sclerosis in SOD1 mice. Frontiers in cellular neuroscience. 2016 May 9;10:117.
22. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. The Journal of clinical investigation. 2012 Apr 2;122(4):1316-38.
23. Kleinridders A, Cai W, Cappellucci L, Ghazarian A, Collins WR, Vienberg SG, Pothos EN, Kahn CR. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. Proceedings of the National Academy of Sciences. 2015 Mar 17;112(11):3463-8.
24. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, Hibbert S, Budnik N, Zampedri L, Dickson J, Li Y. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. The Lancet. 2017 Oct 7;390(10103):1664-75.
25. Billingsley KJ, Barbosa IA, Bandrés-Ciga S, Quinn JP, Bubb VJ, Deshpande C, Botia JA, Reynolds RH, Zhang D, Simpson MA, Blauwendraat C. Mitochondria function associated genes contribute to Parkinson's Disease risk and later age at onset. npj Parkinson's Disease. 2019 May 22;5(1):8.