Immunopathologia Persa
http immunopathol.com
DOI:10.34172/ipp.2025.43986

Efficacy of metformin in the treatment of parkinsonism and depression among diabetic patients type 2

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Received 23 Aug. 2025
Revised: 9 Oct. 2025
Accepted 21 Nov. 2025
ePublished 29 Nov. 2025

Keywords: Metformin, Parkinson's disease, Type 2 diabetes mellitus, Renal protection, Neurological biomarkers, Motor function, Cognitive function, Quality of life, Inflammatory markers

Abstract

Introduction: Parkinson's disease (PD) often coexists with type 2 diabetes mellitus (T2DM), which may worsen disease progression. Metformin, a common diabetes medication, showed potential benefits beyond blood sugar control.

Objectives: This study examines metformin's impact on renal function, neurological biomarkers, and clinical outcomes in patients with both PD and T2DM.

Patients and Methods: This prospective case-control study involved 50 patients with both T2DM and parkinsonism, recruited from Al-Azhar university hospitals in Assiut, Egypt, between August 2024 and August 2025. Participants were divided equally into two groups; a control group receiving their standard treatment for Parkinsonism and diabetes, and a metformin-treated group receiving metformin alongside their usual therapies. Demographic data and laboratory markers were collected at baseline. Disease assessment employed standardized tools such as the unified Parkinson's Disease Rating Scale (UPDRS) for motor function, Beck Depression Inventory (BDI) for depression severity, Hoehn and Yahr scale for disease staging, Montreal Cognitive Assessment (MoCA) for cognitive evaluation, and Parkinson's Disease Questionnaire-39 (PDQ-39) for quality of life (QOL). All assessments were repeated after a 12-month follow-up to analyze changes relative to baseline.

Results: The findings indicated that metformin treatment offers comprehensive benefits by protecting against renal function decline, influencing neurological biomarkers, and supporting multiple clinical domains in PD. It appears to mitigate disease progression, preserve cognitive function, and enhance psychosocial well-being, while having neutral effects on vitamin status and potentially positive, though non-significant, effects on inflammatory markers. Overall, metformin not only prevents typical clinical deterioration but also actively improves motor, cognitive, psychological, and quality-of-life outcomes.

Conclusion: Metformin demonstrates promising multifaceted benefits in PD patients with T2DM by not only protecting renal function and preventing clinical deterioration but also actively improving motor, cognitive, psychological, and quality-of-life outcomes across multiple clinical domains, supporting its consideration as an adjunctive therapeutic strategy pending further research.

Citation: El Nasser WS, Fahmy EM, Helmy AM, Saleh MW, Hassan ASS, Abdelrahman MAM, Hassan HH, Abd El-Hamid B, Fouad S, Etewa MAM, AM T, Mohamed TE, Abo Seif A, Abdella AMM, Abd El-Nabi Atlam R, Hegazy N, Abbas MA, Zeid MY, Mohamed KR, Noureldeen A, Badawy HK. Efficacy of metformin in the treatment of parkinsonism and depression among diabetic patients type 2. Immunopathol Persa. 2026;12(1):e43986. DOI:10.34172/ipp.2025.43986.

Introduction

Type 2 diabetes mellitus (T2DM) represents a major global health challenge, affecting over 400 million individuals worldwide (1) and characterized by progressive insulin resistance and pancreatic β-cell dysfunction (2). The pathophysiology of T2DM involves a complex interplay of genetic and environmental factors, with core mechanisms including chronic hyperglycemia, inflammation, endoplasmic reticulum stress, oxidative stress, and ectopic lipid deposition that collectively contribute to metabolic dysfunction (3). Recent epidemiological evidence demonstrates that T2DM affects 20-50% of patients who develop chronic kidney disease, leading to end-stage kidney disease and substantially increased mortality risk (3,4). The disease is further complicated by its association with multiple comorbidities, including cardiovascular disease, diabetic nephropathy, and an emerging body of evidence linking T2DM to neurodegenerative disorders (1,3). Current therapeutic approaches primarily focus on glycemic control through lifestyle interventions and pharmacological management (5), with metformin serving as the cornerstone first-line treatment due to its efficacy in improving clinical outcomes and reducing complications (1).

Parkinson's disease (PD) represents the second most common neurodegenerative disorder globally (6-8), characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the pathological accumulation of α-synuclein protein aggregates known as Lewy bodies (7). The pathogenesis of PD involves multiple interconnected mechanisms, including mitochondrial dysfunction, oxidative stress, neuroinflammation, protein misfolding and aggregation, and impaired autophagy pathways (6,7,9,10). Neuroinflammation, mediated by microglial activation and the elevation of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), plays a crucial role in PD pathogenesis and is significantly associated with both motor and non-motor symptoms (6). The disease manifests through characteristic motor symptoms, including tremor, rigidity, bradykinesia, and postural instability, alongside non-motor symptoms such as cognitive impairment, sleep disorders, and gastrointestinal dysfunction (11,12). Recent evidence suggests that PD pathology may originate in the gut through α-synuclein mis-folding and spread via prion-like mechanisms through the vagus nerve to the central nervous system, highlighting the importance of the gut-brain axis in disease progression (10,13).

Emerging research shows significant epidemiological and molecular links between T2DM and PD, with T2DM patients showing increased risk for PD development and accelerated disease progression (14-16). The comorbidity between these conditions appears to be mediated through shared pathogenic mechanisms, including insulin resistance, chronic inflammation, mitochondrial dysfunction, and disrupted protein homeostasis (17,18). Metformin, the first-line antidiabetic medication, has been utilized since 1960 (19) and has emerged as a promising therapeutic intervention for PD management in diabetic patients due to its multifaceted neuroprotective properties beyond glycemic control (1, 20, 21). It will be able to improve PD patients' conditions with progressive and debilitating neurological disorders (22). Preclinical studies demonstrate that metformin exerts neuroprotective effects through multiple pathways, including AMP-activated protein kinase (AMPK) activation leading to enhanced autophagy, clearance of pathological α-synuclein aggregates, mitochondrial function improvement, reduction of oxidative stress and neuroinflammation, and normalization of astrocyte senescence (21,23,24). Clinical evidence supports metformin's renoprotective effects in T2DM patients, with significant reductions in major adverse cardiovascular events and major adverse kidney events, while simultaneously modulating neurological biomarkers and improving clinical outcomes in patients with T2DM-PD comorbidity (25). These findings suggest that metformin represents a unique therapeutic opportunity to address both metabolic and neurodegenerative pathologies simultaneously, offering potential disease-modifying effects in this complex patient population.

Key point

In a prospective case-control study, we found that metformin appears to offer a wide range of therapeutic advantages for managing Parkinson's disease (PD) in individuals with type 2 diabetes. Alongside its well-known ability to protect kidney function, metformin favorably modulates neurological biomarkers, helping to maintain and improve both motor and cognitive abilities. The drug also delivers psychosocial and quality-of-life improvements, reflecting benefits across various clinical aspects. Although its influence on inflammatory markers was positive yet not statistically significant, and it did not affect vitamin levels, the evidence overall points to metformin's promising role in both halting disease progression and enhancing multiple patient outcomes. Collectively, these findings provide a strong rationale for considering metformin as an adjunct treatment in PD, emphasizing the need for further studies to validate these effects and clarify underlying mechanisms.

Objectives

The objective of this study was to evaluate the multifaceted effects of metformin on renal function, neurological biomarkers, motor and cognitive outcomes, psychological well-being, and quality of life (QOL) in patients with PD and T2DM, to determine its potential as an adjunctive therapeutic strategy for mitigating disease progression and enhancing clinical outcomes.

Patients and Methods

Study design and participants

This prospective case-control study was conducted on 50 patients diagnosed with both T2DM and parkinsonism,

who were referred to Al-Azhar university hospitals in Assiut, Egypt, between August 2024 and August 2025. The participants were assigned to two equal groups with 25 patients in each group. The control group continued their regular treatment for parkinsonism and diabetes, and the metformin-treated group, which received metformin in addition to their standard treatments for both conditions.

Inclusion criteria

Participants were eligible for inclusion in the study if they met all of the following criteria: a diagnosis of T2DM based on the American Diabetes Association (ADA) criteria; a diagnosis of parkinsonism according to the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) criteria: stable glycemic control, defined as an glycated hemoglobin (HbA1c) level below 8%, maintained on their current diabetes management regimen for at least three months before enrollment; age between 40 and 75 years; and the ability to provide written informed consent.

Exclusion criteria

Participants were excluded from the study if they met any of the following criteria: a diagnosis of PD or other Parkinsonian disorders not solely attributed to diabetes-related causes, as determined by a neurologist; severe or psychotic depression requiring urgent or intensive psychiatric treatment; a history of contraindications to metformin use; ongoing use of medications known to significantly affect parkinsonian or depressive symptoms, such as dopamine agonists, monoamine oxidase inhibitors, tricyclic antidepressants, or selective serotonin reuptake inhibitors, unless the dosage had been stable for at least three months before screening and was expected to remain unchanged throughout the study; presence of other significant neurological or psychiatric comorbidities that, in the judgment of the researchers, might confound the study outcomes; or participation in a similar intervention study within the three months preceding enrollment.

Data collection

At the outset of the study, informed written consent was obtained from all participants, and demographic information, including age, gender, and baseline symptoms, was collected through participant interviews. A 10 mL blood sample was drawn to evaluate laboratory parameters such as HbA1c, vitamin B12, IL-6, estimated glomerular filtration rate (eGFR), creatinine, and alpha-synuclein levels. Multiple standardized questionnaires were administered during interviews to assess various aspects of the disease. The Unified Parkinson's Disease Rating Scale (UPDRS) was utilized to evaluate and monitor PD progression and motor impairment (26). Depression severity was measured using the Beck Depression Inventory (BDI) (27), while the Hoehn and Yahr scale was employed to characterize disease stage and symptom severity (26,28). Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) (29), and QOL was measured using the Parkinson's Disease Questionnaire-39 (PDQ-39) (30). Participants were followed for 12 months, after which all assessments were repeated and compared to baseline values to evaluate changes over time.

UPDRS questionnaires

The UPDRS is divided into four parts: Part I evaluates nonmotor experiences of daily living, including mentation, behavior, and mood; Part II assesses motor experiences of daily living, focusing on the patient's ability to perform everyday tasks; Part III is a clinician-scored motor examination assessing motor function; and Part IV addresses motor complications related to therapy. Each item within these parts is rated on a scale from 0 (normal) to 4 (severe). The total score for each part is obtained by summing the corresponding item scores, with higher scores indicating greater disability (26).

MoCA questionnaire

The MoCA/30 is scored on a scale from zero to 30 points, with the total score representing the overall cognitive function. A score of 26 or above is considered normal cognitive performance. Scores below 26 suggest varying degrees of cognitive impairment: 18 to 25 indicates mild cognitive impairment, 10 to 17 signifies moderate cognitive impairment, and fewer than 10 points reflect severe cognitive impairment (29).

Hoehn and Yahr scale

The Hoehn and Yahr scale is a widely used clinical tool for describing the progression and severity of PD symptoms (28). It categorizes the disease into stages based on the extent of motor impairment and functional disability. The original scale includes five stages: Stage 1 indicates mild symptoms with unilateral involvement and minimal or no functional disability; Stage 2 shows bilateral involvement without balance impairment; Stage 3 represents the onset of postural instability with mild to moderate disability, though the patient remains physically independent; Stage 4 is marked by severe disability but the patient can still walk or stand unassisted; and Stage 5 indicates the most advanced stage with confinement to a wheelchair or bed unless aided (26,28).

QOL assessment

The QOL in parkinsonism was assessed using the PDQ-39, a widely used, patient-reported instrument designed to evaluate the impact of PD on daily functioning and well-being (30). The PDQ-39 consists of 39 items grouped across eight dimensions of QOL: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Patients respond to each item based on how often they have experienced specific difficulties related to Parkinson's

over the past month, using a five-point Likert scale ranging from "never" to "always." The responses are then summed and transformed into scores for each dimension on a 0 to 100 scale, with higher scores indicating greater impairment (30).

BDI questionnaires

The BDI questionnaire consists of 21 multiple-choice items, each scored on a scale from 0 to 3 based on the severity of symptoms, with 0 indicating no symptoms and 3 indicating severe symptoms. The total score ranges from 0 to 63, and higher scores indicate more severe depressive symptoms. The standard interpretation of the total BDI score is as follows: 0–9 indicates minimal depression, 10–18 mild depression, 19–29 moderate depression, and 30–63 severe depression (27).

Data analysis

Data analyses were conducted using Statistical Package for Social Sciences (SPSS) software version 27 (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was employed to evaluate the normality of the data. While both parametric and non-parametric methods were initially considered, parametric tests were ultimately chosen due to their greater accuracy and reliability in hypothesis testing, as both approaches produced similar *P* values for all variables analyzed. Statistical analyses, including the chi-square test, Fisher's exact test, independent T-test, paired T-test, and McNemar's test, were performed to compare variables between the control and metformin-treated groups at baseline and at the 12-month follow-up, as well as to assess within-group changes from baseline to 12 months.

Results

The comparative analysis between the control and metformin treatment groups revealed comparable demographic distributions and baseline symptom profiles across both study populations. Gender distribution showed near-equal representation between males and females in both groups. Age characteristics demonstrated similarity between groups, with participants presenting within comparable age ranges typical of the study population. Baseline glycemic control, as measured by HbA1c levels, showed consistent values between the control and metformin groups, indicating similar metabolic status at study initiation. Regarding baseline gastrointestinal symptoms, the majority of participants in both groups reported no diarrhea symptoms at baseline, though a small proportion in each group experienced this symptom. Nausea symptoms followed a similar pattern, with most participants in both treatment arms reporting absence of this symptom at baseline, while a minority presented with nausea complaints. Notably, lactic acidosis was absent in all participants across both study groups at baseline, representing a consistent finding. The statistical analyses revealed no significant differences between groups for any of the measured demographic characteristics or baseline symptoms (Table 1).

Throughout the study period, the comparison of laboratory parameters in the metformin-treated group and the control group demonstrated that vitamin B12 levels remained relatively stable in both groups over time, with no significant changes observed. The inflammatory marker IL-6 demonstrated a significant increase from baseline to the end of the study in the control group, while it remained stable in the metformin group. Kidney function, as assessed by eGFR, decreased significantly in the control group throughout the study, whereas it was preserved in the metformin-treated group. Serum creatinine levels increased significantly in the control group but showed no significant change in the metformin group during the same period. Additionally, alpha-synuclein levels were decreased over time in the control group; however, it was remained relatively unchanged in the metformin group. In terms of the between-groups comparison, the vitamin B12, alpha synuclein, and creatinine levels showed no statistically significant differences between the treatment

Table 1. Comparison of demographic characteristics and baseline symptoms between case and control groups

Demographic characteristics and baseline symptoms		Group				*P* value
		Control (n = 25)		Metformin (n = 25)		
		No.	%	No.	%	
Gender	Male	13	52	12	48	0.777*
	Female	12	48	13	52	
Diarrhea	No	23	92	21	84	0.384*
	Yes	2	8	4	16	
Lactic acidosis	No	25	100	25	100	a
	Yes	0	0	0	0	
Nausea	No	20	80	21	84	0.713*
	Yes	5	20	4	16	
Variable		**Mean**	**SD**	**Mean**	**SD**	***P*-value**
Age (year)		66.32	2.68	65.48	5.97	0.526**
HbA1c (%)		6.68	024	6.73	0.23	0.489**

HbA1c: Glycated hemoglobin; SD: standard deviation.
*Chi-square, **Independent T-test, a: No statistics applied.

and control cohorts at either baseline or 12 months follow-up. Interleukin-6 concentrations showed divergent trajectories between the groups, with the control group experiencing an increase over time while the metformin group maintained relatively stable levels, resulting in a statistically significant difference at the twelve-month mark. The eGFR demonstrated contrasting changes, as the control group showed a decline in kidney function over the study period while the metformin group maintained better renal function, leading to a statistically significant difference at follow-up despite similar baseline values (Table 2).

The analysis of parameter changes from baseline to twelve months revealed distinct patterns between the metformin-treated and control groups. Vitamin B12 levels demonstrated comparable modest increases in both groups over the study period, with no statistically significant difference in the magnitude of change between the treatment groups. Interleukin-6 changes showed contrasting directions, as the control group experienced an increase while the metformin group showed a slight decrease, though this difference did not reach statistical significance. The most pronounced divergence occurred in the eGFR, where the control group exhibited a decline in renal function while the metformin group demonstrated an improvement, resulting in a statistically significant difference in change patterns between the groups. Creatinine changes followed a similar trend to eGFR but in the opposite direction, with the control group showing a greater increase compared to the metformin group, though this difference approached but did not achieve statistical significance. Alpha synuclein changes revealed significantly different trajectories, with the control group showing a decrease while the metformin group demonstrated an increase over the study period (Table 3).

Throughout the study period, individuals treated with metformin demonstrated clinical advantages across several domains compared to those in the control group. While both groups started with comparable scores for motor impairment, cognition, QOL, and depression, the metformin group exhibited notably greater improvements over time, particularly in motor performance and cognitive abilities. The progression of PD symptoms appeared less pronounced in the metformin group, reflected in measures

Table 2. Comparison of laboratory parameters in metformin-treated versus control groups throughout the study period

Laboratory parameters		Group				*P* value*
		Control (n = 25)		Metformin (n = 25)		
		Mean	SD	Mean	SD	
Vitamin B12 (pg/mL)	Baseline	398.5	31.94	412.94	38.19	0.153
	After 12-months	401.16	31.33	415.86	38.73	0.147
	P value**	0.077		0.793		
IL-6 (pg/mL)	Baseline	5.25	0.81	4.89	1.13	0.197
	After 12-months	5.70	0.89	4.80	1.51	0.014
	P value**	0.018		0.808		
eGFR (mL/min/1.73m²)	Baseline	87.06	7.07	86.44	8.55	0.784
	After 12-months	78.88	6.36	88.01	12.16	0.002
	P value**	<0.001		0.601		
Creatinine (mg/dL)	Baseline	0.97	0.14	1.01	0.19	0.615
	After 12-months	1.07	0.15	1.02	0.17	0.273
	P value**	<0.001		0.579		
Alpha synuclein (ng/mL)	Baseline	1.90	0.23	1.75	0.28	0.037
	After 12-months	1.74	0.20	1.83	0.29	0.232
	P value**	<0.001		0.335		

IL-6: Interleukin 6; eGFR: Estimated glomerular filtration rate; SD: Standard deviation. *Independent T-test, **Paired T-test.

Table 3. Comparison of laboratory parameter changes over study time (After 12 months versus baseline) between the metformin-treated and control groups

Laboratory parameters	Group		Difference between groups	*P* value*
	Control (n = 25)	Metformin (n = 25)		
	Mean difference	Mean difference		
Vitamin B12 (pg/mL)	+2.66	+2.91	0.25	0.982
IL-6 (pg/mL)	+0.44	-0.09	0.53	0.209
eGFR (mL/min/1.73m²)	-8.17	+1.55	9.72	0.003
Creatinine (mg/dL)	+0.09	+0.02	0.07	0.090
Alpha synuclein (ng/mL)	-0.16	+0.08	0.024	0.007

IL-6: Interleukin 6; eGFR: Estimated glomerular filtration rate; SD: Standard deviation. *Independent T-test.

assessing disease severity and depression, with their levels remaining significantly more favorable than those seen in controls. QOL ratings also showed a tendency toward stabilization or improvement among metformin recipients, whereas controls tended to experience declines. Regarding categorical staging of PD, differences between groups emerged but were less marked than other clinical indicators, with medication exposure associated with a shift toward earlier stages or slower progression (Table 4).

The longitudinal changes observed throughout the study period revealed markedly divergent clinical trajectories between the metformin-treated and control groups across all measured domains. While the control group experienced deterioration in motor function, the metformin group demonstrated notable improvement, resulting in a clinically meaningful difference between the treatment arms. Cognitive performance followed a similar pattern, with controls showing minimal enhancement compared to the substantial cognitive gains observed in the metformin recipients. QOL measures revealed contrasting directions of change, with controls experiencing decline while the metformin group achieved improvement, creating a significant differential benefit favoring the treatment group. Depression scores similarly diverged, with controls showing worsening depressive symptoms over time while the metformin group exhibited marked improvement in mood-related outcomes (Table 5).

Discussion

Our study findings indicated that metformin treatment might provide protective effects against renal function decline and influence neurological biomarker dynamics while having neutral effects on vitamin B12 status and potentially beneficial but non-significant effects on

Table 4. Comparison of motor impairment score, cognitive abilities, severity of Parkinson's disease symptoms, depression, and QOL score in metformin-treated versus control groups throughout the study period

Variable	Time	Group				*P* value*
		Control (N = 25)		Metformin (N = 25)		
		Mean	SD	Mean	SD	
UPDRS score	Baseline	29.23	5.06	30.40	5.11	0.423
	After 12-months	30.11	4.93	27.15	4.11	0.025
	P value**	0.384		0.045		
MoCA/30 score	Baseline	24.01	2.66	23.66	2.59	0.639
	After 12-months	24.40	2.99	26.49	3.46	0.028
	P value**	0.623		0.004		
QOL score	Baseline	60.86	9.26	62.34	7.50	0.537
	After 12-months	61.70	9.09	58.34	9.70	0.213
	P value**	0.032		0.125		
BDI score	Baseline	20.92	2.19	21.46	2.41	0.280
	After 12-months	23.54	30.01	18.20	2.02	<0.001
	P value**	<0.001		<0.001		
Variable		**Control (n = 25)**		**Metformin (n = 25)**		***P* value**
		No.	**%**	**No.**	**%**	
Hoehn-Yahr stage	Baseline Stage 1	4	16	4	16	0.318***
	Baseline Stage 2	7	28	12	48	
	Baseline Stage 3	14	56	9	36	
	After 12-months Stage 1	3	12	7	28	0.142****
	After 12-months Stage 2	14	56	15	60	
	After 12-months Stage 3	8	32	3	12	
	P value*****	0.139		0.067		

UPDRS: Unified Parkinson›s Disease Rating Scale; MoCA: Montreal Cognitive Assessment; QOL: Quality of life; BDI: Beck Depression Inventory; SD: standard deviation. *Independent T-test, **Paired T-test, ***Fishers' exact test, ****Chi-square, *****McNemar.

Table 5. Comparison of the changes in motor impairment score, cognitive abilities, depression, and QOL score throughout the study (after 12 months versus baseline) between the metformin-treated and control groups

Variable	Group		Difference between groups	*P* value*
	Control (n = 25)	Metformin (n = 25)		
	Mean difference	Mean difference		
UPDRS Score	+0.88	-3.24	4.12	0.029
MoCA/30 score	+0.39	+2.82	2.43	0.047
QOL score	+0.84	-3.99	4.83	0.013
BDI score	+2.52	-3.44	5.96	<0.001

UPDRS: Unified Parkinson›s Disease Rating Scale; MoCA: Montreal Cognitive Assessment; QOL: Quality of life; BDI: Beck Depression Inventory.
*Independent T-test.

inflammatory markers. These findings align with several previous studies. Large-scale epidemiological and clinical studies have reported metformin's neuroprotective potential in patients with T2DM, highlighting its ability to attenuate neurodegenerative pathways implicated in PD, such as mitochondrial dysfunction, insulin resistance, and neuroinflammation (17,18). However, an observational study by Huang et al has shown mixed results on metformin's association with PD risk, with dose-dependent effects where lower cumulative doses may reduce PD odds, but higher doses do not confer protection or might increase risk (31). Conversely, a meta-analysis by Qin et al found no significant association between metformin use and the risk of PD (32). Furthermore, metformin's renoprotective profile has been acknowledged, consistent with its beneficial effects on renal biomarkers in diabetic populations (33). Corremans et al reported in their study that metformin has beneficial effects on kidney function (34). Notably, our observation of neutral effects on vitamin B12 status concurs with reports that vitamin deficiency can be a concern in T2DM patients; Fituri et al found that metformin treatment has been shown to negatively impact serum vitamin B12 levels in patients with T2DM (35). An observational study consistent with our findings reported no significant reduction in vitamin B12 levels at 6, 12, 24, or 36 months in pediatric patients undergoing metformin treatment (36). This finding, suggesting that metformin has potentially beneficial yet statistically non-significant effects on inflammatory markers, contrasts with the study by Chen et al, which reported that metformin significantly reduces inflammatory markers such as IL-6 in patients with T2DM (37). An animal study also demonstrated that metformin attenuates the inflammatory response by downregulating the expression of proinflammatory cytokines, including IL-6 (38).

In the overall context of PD management among patients with T2DM, our results emphasize metformin's multidimensional therapeutic potential. By demonstrating stabilization of renal function alongside favorable shifts in clinical outcomes, such as maintaining vitamin B12 and inflammation status, our study contributes robust prospective evidence supporting metformin's role beyond glycemic control. This complements insights from preclinical and clinical research that link metformin's modulation of mitochondrial activity, autophagy, and inflammation with attenuation of PD progression (39). Although inflammatory markers showed non-significant but positive trends, such subtle immunomodulatory effects may be relevant since chronic inflammation is a shared pathophysiological feature of PD and T2DM (40).

Overall, our study adds to the growing body of literature that supports metformin's potential benefits in managing PD in patients with T2DM. By preserving renal function, maintaining vitamin status, and positively influencing neurological biomarkers and clinical outcomes, metformin emerges as a promising candidate for multifaceted disease modification. Nonetheless, given the mixed evidence regarding dose-related effects and PD risk, further large-scale randomized controlled trials with well-characterized dosing regimens and biomarker analysis are warranted to optimize treatment protocols and fully elucidate metformin's neuroprotective mechanisms. These findings advocate for metformin's integration as an adjunctive therapeutic strategy in this comorbid population, addressing complex metabolic interactions.

Our study results also demonstrated that metformin treatment in T2DM patients might confer holistic benefits, mitigating disease progression by decreasing motor impairment, preserving cognitive capacity, improving psychosocial well-being and reducing depression, and improving QOL among individuals with PD compared to standard care. These findings align with emerging evidence from recent clinical studies, though the literature presents complex and sometimes contradictory results. Recent meta-analyses by Qin et al revealed mixed outcomes regarding metformin's association with PD risk, with some studies showing increased risk (HR, 1.50; 95% CI, 1.11 to 2.02) when analyzing pooled data (32), while others demonstrated protective effects at lower dosages. Huang et al found that patients receiving <300 cumulative defined daily doses of metformin had significantly lower odds of developing PD (OR 0.88; 95% CI, 0.83–0.94), suggesting a dose-dependent relationship (31). The neuroprotective mechanisms demonstrated in preclinical studies by Mor et al support the current findings, showing that metformin reduces mitochondrial hyperactivity and improves both motor function and neuronal viability in *Caenorhabditis elegans* models (41). Our finding that metformin enhances cognitive abilities in patients with T2DM and PD aligns with the study by Markowicz-Piasecka et al, which demonstrates that long-term metformin use in diabetic patients is associated with improved cognitive function (42). Shi et al found in their study that long-term metformin use significantly reduces the risk of neurodegenerative diseases (43). Improvement in depression and QOL following metformin treatment is another one of our findings, consistent with previous studies. A study by Molteni et al demonstrated that metformin use enhances the QOL in patients with T2DM (44). Recently, Qaisar et al found that metformin enhances the QOL related to sarcopenia in elderly adults (45). In a review study, Cheng et al concluded that metformin contributes to the reduction of depressive symptoms after analyzing multiple studies (46). Several animal studies have provided additional evidence supporting the effectiveness of metformin in alleviating depressive symptoms, demonstrating its potential as a therapeutic agent for mood disorders in preclinical models (47).

Overall, the present study's findings contribute significantly to the growing body of evidence supporting the repurposing of antidiabetic medications for neurodegenerative diseases, particularly in the context

of T2DM-PD comorbidity. The demonstrated holistic benefits of metformin treatment, encompassing motor improvement, cognitive preservation, reduced depression, and enhanced QOL, represent a substantial advancement over standard care approaches and align with the emerging paradigm of metabolic-based neuroprotection. These results are consistent with preclinical evidence demonstrating metformin's neuroprotective mechanisms and complement clinical findings from glucagon-like peptide-1 receptor agonist trials, suggesting that targeting metabolic dysfunction may represent a viable strategy for disease modification in PD.

Conclusion

In conclusion, metformin demonstrates promising multifaceted benefits in the management of PD in patients with T2DM. Beyond its well-established renal protective effects, metformin positively influences neurological biomarkers and contributes to the stabilization and improvement of motor and cognitive functions. It also offers psychological and quality-of-life enhancements, suggesting a broad impact across clinical domains. While its effects on inflammatory markers are favorable but not statistically significant, and vitamin status remains unaffected, the overall findings highlight metformin's potential not only in preventing clinical deterioration but also in actively enhancing patient outcomes across several dimensions. These results support the consideration of metformin as an adjunctive therapeutic strategy in PD, warranting further research for confirmation and mechanistic exploration.

Limitations of the study

This study has several limitations that should be considered regarding the interpretation of results. The sample size was relatively small, with only 50 participants divided equally between two groups, which may limit the generalizability of the findings and reduce statistical power to detect subtle effects. The study was conducted at a single center in Assiut, Egypt, potentially limiting the applicability of results to broader or more diverse populations. Additionally, the follow-up period of 12 months, while adequate for some outcomes, may be insufficient to capture the long-term effects of metformin on parkinsonism and diabetes-related variables. The exclusion of patients with more severe psychiatric or neurological conditions could introduce selection bias and limit understanding of metformin's effects in more complex cases. Furthermore, reliance on self-reported measures and questionnaires may be subject to participant bias or inaccuracies. Lastly, although efforts were made to control for confounding medications, complete control over all external factors affecting Parkinsonian and depressive symptoms is challenging in clinical studies, which could influence the results.

Acknowledgments

The authors would like to express their sincere gratitude to the patients who participated in this study, as well as to the medical and administrative staff at Al-Azhar University Hospitals in Assiut, Egypt, for their invaluable support and assistance.

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Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The study was conducted under the principles of the Declaration of Helsinki. Informed written consent was obtained from all participants. This study resulted from research that was registered in August 2024 (No: RESEARCH/AZ.AST/MED018/4/234/8/2024) and approved by the ethics committee of the Faculty of Medicine, Al-Azhar University (Assiut), Egypt. Additionally, the authors have thoroughly addressed ethical issues, including plagiarism, data fabrication, and double publication.

Funding/Support

The authors did not receive any source of funding.

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