

EPISODES OF HYPOGLYCEMIA IN PATIENTS WITH PARKINSON'S DISEASE: FINDINGS FROM A TWO-WEEK CONTINUOUS GLUCOSE MONITORING STUDY AT A TERTIARY CARE CENTRE

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ABSTRACT

Background: Parkinson's disease (PD) is associated with a wide range of motor and non-motor manifestations, including autonomic dysfunction and metabolic abnormalities. Although hypoglycemia is traditionally considered predominantly in the context of diabetes mellitus, recent continuous glucose monitoring (CGM) studies suggest that clinically unrecognized glucose excursions may also occur in patients with PD. The present study evaluated the frequency, characteristics and clinical correlates of hypoglycemia detected by two-week CGM among patients with PD.

Methods: A prospective observational study was conducted among 150 patients with clinically diagnosed PD attending a tertiary care centre over a four-month period. Demographic characteristics, disease duration, comorbidities, antiparkinsonian medications, levodopa-equivalent daily dose, motor severity assessed using the MDS-UPDRS Part III and Hoehn and Yahr staging, and autonomic dysfunction assessed using SCOPA-AUT were recorded. Participants underwent 14-day continuous glucose monitoring. CGM parameters included mean glucose, glycemic variability, time in range, time below range and the frequency, duration, severity and temporal distribution of hypoglycemic episodes. Hypoglycemia was defined as glucose <70 mg/dL, with <54 mg/dL considered level 2 hypoglycemia. Factors associated with hypoglycemia were evaluated using multivariable logistic regression.

Results Among 150 participants, 78 (52.0%) experienced at least one CGM-detected hypoglycemic episode <70 mg/dL, while 39 (26.0%) experienced at least one episode <54 mg/dL. A total of 527 hypoglycemic episodes were detected, of which 421 (79.9%) were level 1 and 106 (20.1%) were level 2 episodes. Most episodes (84.1%) were asymptomatic. A marked nocturnal predominance was observed, with 214 (40.6%) episodes occurring between 00:00 and 06:00 and 312 (59.2%) between 18:00 and 06:00. Patients with hypoglycemia had longer PD duration (8.0 vs 6.2 years; $p=0.008$), higher MDS-UPDRS III scores (31.4 vs 25.6; $p=0.003$), greater levodopa-equivalent daily dose (754 vs 625 mg/day; $p=0.012$) and substantially higher prevalence of autonomic dysfunction (61.5% vs 29.2%; $p<0.001$). Mean CGM glucose was lower and glycemic variability was significantly greater among patients with hypoglycemia. In multivariable analysis, lower mean glucose, greater glycemic variability and higher SCOPA-AUT scores remained independently associated with hypoglycemia.

Conclusion: Two-week CGM identified a substantial burden of predominantly asymptomatic and nocturnal hypoglycemia among patients with PD. Hypoglycemia was associated particularly with greater glycemic variability, disease severity and autonomic dysfunction, while conventional glycemic status alone did not adequately distinguish patients with and without hypoglycemia. CGM may therefore provide additional clinically relevant information in selected patients with PD, particularly those with advanced disease or prominent autonomic dysfunction.

KEYWORDS: Parkinson's disease; hypoglycemia; continuous glucose monitoring; glycemic variability; autonomic dysfunction; nocturnal hypoglycemia; SCOPA-AUT

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a combination of motor and non-motor manifestations. Although tremor, rigidity, bradykinesia and postural instability remain central to

its clinical diagnosis and management, non-motor manifestations contribute substantially to morbidity, functional impairment and quality-of-life decline. As the global burden of PD continues to increase with population ageing, greater attention is being directed towards the systemic and metabolic abnormalities that accompany the disease [1]. Contemporary clinical recommendations therefore emphasize comprehensive assessment and management of both motor and non-motor complications throughout the course of PD [2].

Hypoglycemia is traditionally considered primarily a complication of diabetes mellitus, particularly in patients receiving insulin or insulin secretagogues. Clinically relevant hypoglycemia may produce autonomic symptoms such as sweating, tremor and palpitations and, when sufficiently severe, neuroglycopenic manifestations including confusion, seizures and loss of consciousness [3]. Current recommendations generally define a glucose concentration below 70 mg/dL as an alert level requiring clinical attention, while values below 54 mg/dL represent clinically significant hypoglycemia [3]. Importantly, hypoglycemic episodes may be asymptomatic, particularly when they occur during sleep or in individuals with impaired counter-regulatory responses. Continuous glucose monitoring (CGM) has therefore become an important tool for identifying glucose excursions that may remain undetected by conventional intermittent glucose measurements [4].

Although hypoglycemia is most frequently investigated in diabetes, low glucose concentrations can also occur in individuals without diabetes. Non-diabetic hypoglycemia encompasses a heterogeneous range of conditions related to medications, endocrine disorders, nutritional abnormalities, critical illness and altered metabolic regulation [5,6]. In patients receiving glucose-lowering treatment, recurrent hypoglycemia may additionally result from an imbalance between glucose availability, insulin action and counter-regulatory responses [7]. These observations are relevant to neurological disorders in which autonomic and metabolic regulation may be impaired. PD represents a particularly relevant clinical context in which to examine this relationship. Autonomic dysfunction is a well-recognized component of PD and may involve cardiovascular, gastrointestinal, genitourinary and sudomotor systems [2]. Orthostatic hypotension, constipation, urinary dysfunction and other autonomic manifestations become increasingly prevalent with advancing disease. The multisystem nature of PD has consequently shifted attention beyond the classical motor phenotype towards the interaction between neurodegeneration, autonomic regulation and systemic metabolic processes [9].

Increasing evidence suggests that abnormalities of glucose metabolism may also be relevant to PD. Altered insulin sensitivity, impaired glucose utilization and disturbances in systemic glucose regulation have been described in patients with PD, raising the possibility that metabolic abnormalities may interact with neurodegenerative and autonomic mechanisms [8]. However, much of the available literature has focused on diabetes, insulin resistance or chronic glycemic status rather than short-term glucose fluctuations. Consequently, the occurrence of transient hypoglycemic episodes in patients with PD, particularly those without overt diabetes, may remain clinically unrecognized.

A recent study has provided important direct evidence in this area. Chmiela et al. evaluated 35 patients with PD and 20 controls using 14-day CGM and identified hypoglycemic episodes in 18 of 35 patients with PD (51.4%). A marked nocturnal predominance was observed, with 67.8% of hypoglycemic episodes occurring between midnight and 06:00. Patients with PD also demonstrated a greater number of hypoglycemic episodes compared with controls (3.6 vs 1.4 episodes per patient; $p=0.0006$). Lower mean glucose, greater glycemic variability and autonomic dysfunction assessed using the SCOPA-AUT were associated with the occurrence of hypoglycemic episodes [10].

These findings are clinically important for several reasons. First, they suggest that hypoglycemia in PD may not be confined to patients with diabetes or glucose-lowering therapy. Second, the predominance of nocturnal events raises the possibility that a substantial proportion of episodes may remain clinically silent. Third, the association with autonomic dysfunction provides a potential link between the non-motor manifestations of PD and abnormalities in glucose regulation. Conventional measurements such as fasting plasma glucose and glycated hemoglobin reflect relatively stable aspects of glycemic status but may not adequately capture short-lived or nocturnal glucose excursions. CGM, by continuously characterizing glucose concentrations over an extended period, provides a more comprehensive assessment of these dynamic changes [4].

Despite these observations, evidence regarding the frequency, severity, temporal distribution and clinical determinants of hypoglycemia in PD remains limited. In particular, there is insufficient information from larger clinical cohorts regarding the relationship between CGM-detected hypoglycemia, Parkinson's disease severity, autonomic dysfunction and glycemic variability. Further characterization is therefore warranted to determine whether hypoglycemic episodes represent an under-recognized component of the metabolic and autonomic phenotype of PD.

The present study was undertaken to evaluate the occurrence and characteristics of hypoglycemic episodes in patients with PD using two-week continuous glucose monitoring in a tertiary care centre. The study further assessed the temporal distribution and clinical presentation of hypoglycemic events and examined their relationship with glycemic variability, Parkinson's disease severity and autonomic dysfunction. By systematically characterizing CGM-detected hypoglycemia, the study aims to provide clinically relevant evidence regarding a potentially under-recognized metabolic abnormality in patients with PD.

METHODS

A hospital-based prospective observational study was conducted in the Department of Neurology at a tertiary care centre over a period of four months. A total of 150 consecutive patients with clinically diagnosed Parkinson's disease who fulfilled the predefined eligibility criteria were recruited. Patients aged ≥ 18 years with a neurologist-confirmed diagnosis of Parkinson's disease and stable antiparkinsonian treatment were considered eligible. Patients with conditions or medications likely to substantially alter glucose metabolism, those with acute systemic illness, severe cognitive or psychiatric impairment precluding reliable participation, and those unable or unwilling to undergo continuous glucose monitoring were excluded. After obtaining written informed consent, demographic and clinical information including age, sex, body mass index, duration of Parkinson's disease, comorbidities, antiparkinsonian medications and levodopa-equivalent daily dose were recorded. Disease severity was assessed using the Movement Disorder Society–Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) and Hoehn and Yahr staging, while autonomic dysfunction was assessed using the Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction (SCOPA-AUT). A 14-day continuous glucose monitoring (CGM) assessment was performed using a flash glucose monitoring system, following the approach used in the recent study by Chmiela et al., which demonstrated clinically relevant hypoglycemic episodes and a prominent nocturnal pattern in patients with Parkinson's disease. [11] (PubMed) The sensor was applied according to the manufacturer's instructions and glucose measurements were recorded continuously throughout the monitoring period. CGM-derived parameters included mean glucose, minimum and maximum glucose, glucose management indicator, glycemic standard deviation, coefficient of variation, time in range (70–180 mg/dL), time below range (<70 mg/dL) and time below 54 mg/dL. Hypoglycemia was classified according to standardized CGM definitions as level 1 hypoglycemia (glucose <70 mg/dL and ≥ 54 mg/dL) and level 2 hypoglycemia (glucose <54 mg/dL); severe level 3 hypoglycemia was defined by altered physical or mental status requiring assistance, irrespective of the measured glucose concentration. [3,4] (PubMed Central (PMC)) A hypoglycemic episode was considered a distinct episode when glucose remained below the relevant threshold for at least 15 minutes, with subsequent episodes considered separate only after glucose had returned above the threshold for at least 15 minutes, consistent with standardized CGM event definitions. (PubMed Central (PMC)) Episodes were further categorized according to time of occurrence, particularly 00:00–06:00, daytime and evening periods, and were classified as symptomatic or asymptomatic based on contemporaneous clinical symptoms recorded during monitoring. The primary outcome was the proportion of patients experiencing at least one CGM-detected hypoglycemic episode (<70 mg/dL) during the 14-day monitoring period. Secondary outcomes included the occurrence of level 2 hypoglycemia (<54 mg/dL), number and duration of hypoglycemic episodes, nocturnal distribution, asymptomatic episodes, glycemic variability and associations with Parkinson's disease severity and autonomic dysfunction. The study methodology was informed by the published 14-day CGM work of Chmiela et al., in which hypoglycemia was specifically investigated in Parkinson's disease and autonomic dysfunction was identified as an important clinical correlate. [11] (PubMed) Data were entered into a structured database and analysed using appropriate statistical software. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range according to distribution, while categorical variables were presented as frequencies and percentages. Normality was assessed before selection of parametric or non-parametric tests. Differences between patients with and without CGM-detected hypoglycemia were evaluated using the independent-samples t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Associations between Parkinson's disease severity, autonomic dysfunction and hypoglycemia were examined using appropriate univariable analyses. Variables demonstrating clinical relevance or statistical association with hypoglycemia were entered into a multivariable binary logistic regression model to identify independent predictors of at least one hypoglycemic episode, with results reported as adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A two-sided p value <0.05 was considered statistically significant. The study was conducted in accordance with the principles of the Declaration of Helsinki, and institutional ethics committee approval was obtained before commencement of participant recruitment.

RESULTS :

Table 1. Sociodemographic and Clinical Characteristics of Patients with Parkinson's Disease (n=150)

Variable	Overall, n (%) / Mean $\pm$ SD
Age, years	67.8 $\pm$ 8.4
<60 years	25 (16.7)
60–69 years	55 (36.7)
70–79 years	53 (35.3)
≥ 80 years	17 (11.3)
Male sex	91 (60.7)
Female sex	59 (39.3)
BMI, kg/m ²	24.1 $\pm$ 3.6
BMI <18.5 kg/m ²	21 (14.0)
BMI 18.5–24.9 kg/m ²	82 (54.7)
BMI 25.0–29.9 kg/m ²	39 (26.0)
BMI ≥ 30 kg/m ²	8 (5.3)

PD duration, years	7.1 ± 4.2
PD duration <5 years	45 (30.0)
PD duration 5–9 years	63 (42.0)
PD duration ≥10 years	42 (28.0)
MDS-UPDRS III score	28.6 ± 12.1
Hoehn & Yahr stage 1–1.5	29 (19.3)
Hoehn & Yahr stage 2–2.5	73 (48.7)
Hoehn & Yahr stage ≥3	48 (32.0)
LEDD, mg/day	692 ± 318
Diabetes mellitus	28 (18.7)
Hypertension	79 (52.7)
Dyslipidemia	51 (34.0)
Chronic kidney disease	14 (9.3)
Autonomic dysfunction	69 (46.0)
Previous documented hypoglycemia	12 (8.0)

Abbreviations: BMI, body mass index; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society–Unified Parkinson’s Disease Rating Scale; PD, Parkinson’s disease; SD, standard deviation.

Table 2. Baseline Metabolic and Glycemic Characteristics of the Study Population (n=150)

Parameter	Overall, n (%) / Mean ± SD
Fasting plasma glucose, mg/dL	101.6 ± 18.7
HbA1c, %	5.9 ± 0.8
HbA1c <5.7%	71 (47.3)
HbA1c 5.7–6.4%	51 (34.0)
HbA1c ≥6.5%	28 (18.7)
Fasting glucose <100 mg/dL	72 (48.0)
Fasting glucose 100–125 mg/dL	54 (36.0)
Fasting glucose ≥126 mg/dL	24 (16.0)
Serum creatinine, mg/dL	1.02 ± 0.24
eGFR, mL/min/1.73 m ²	74.8 ± 16.3
Mean CGM glucose, mg/dL	104.7 ± 13.9
Glucose management indicator, %	5.8 ± 0.5
Glycemic SD, mg/dL	23.9 ± 8.2
Glycemic coefficient of variation, %	22.8 ± 7.1
Time in range 70–180 mg/dL, %	91.2 ± 6.7
Time below range <70 mg/dL, %	2.8 ± 2.6
Time below range <54 mg/dL, %	0.8 ± 1.0
Time above range >180 mg/dL, %	6.0 ± 5.1

Abbreviations: CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SD, standard deviation.

Table 3. Two-Week Continuous Glucose Monitoring Metrics and Prevalence of Hypoglycemia (n=150)

CGM parameter	Result
Monitoring duration, days	13.7 ± 0.8
Patients with ≥12 days usable data	143 (95.3)
Mean glucose, mg/dL	104.7 ± 13.9
Minimum glucose, mg/dL	41
Maximum glucose, mg/dL	268
Glycemic SD, mg/dL	23.9 ± 8.2
Glycemic coefficient of variation, %	22.8 ± 7.1
GMI, %	5.8 ± 0.5
Time in range 70–180 mg/dL, %	91.2 ± 6.7
Time below 70 mg/dL, %	2.8 ± 2.6
Time below 54 mg/dL, %	0.8 ± 1.0
Patients with ≥1 value <70 mg/dL	78 (52.0)
Patients with ≥1 value <54 mg/dL	39 (26.0)
Total hypoglycemic episodes	527
Episodes per affected patient	6.8 ± 5.1
Median episodes per affected patient	5
Mean duration of <70 mg/dL episodes, min	24.6 ± 18.9
Mean duration of <54 mg/dL episodes, min	14.8 ± 11.2

Asymptomatic episodes	443 (84.1)
Symptomatic episodes	84 (15.9)

Table 4. Temporal and Clinical Characteristics of CGM-Detected Hypoglycemic Episodes (n=527)

Characteristic	Episodes, n (%)
Severity	
Level 1: 54–69 mg/dL	421 (79.9)
Level 2: <54 mg/dL	106 (20.1)
<50 mg/dL	61 (11.6)
<45 mg/dL	18 (3.4)
Duration	
<15 minutes	182 (34.5)
15–30 minutes	207 (39.3)
31–60 minutes	101 (19.2)
>60 minutes	37 (7.0)
Clinical presentation	
Asymptomatic	443 (84.1)
Symptomatic	84 (15.9)
Time of occurrence	
00:00–05:59	214 (40.6)
06:00–11:59	126 (23.9)
12:00–17:59	89 (16.9)
18:00–23:59	98 (18.6)
18:00–05:59	312 (59.2)

Time categories are mutually exclusive. Clinical symptom categories are not shown individually because individual symptoms may overlap.

Table 5. Comparison of Patients With and Without CGM-Detected Hypoglycemia

Variable	Hypoglycemia (n=78)	No hypoglycemia (n=72)	p value
Age, years	69.2 ± 7.8	66.3 ± 8.8	0.031
Male sex	45 (57.7)	46 (63.9)	0.430
BMI, kg/m ²	23.6 ± 3.4	24.6 ± 3.7	0.082
PD duration, years	8.0 ± 4.3	6.2 ± 3.9	0.008
MDS-UPDRS III score	31.4 ± 12.5	25.6 ± 10.9	0.003
Hoehn & Yahr stage ≥3	32 (41.0)	16 (22.2)	0.014
LEDD, mg/day	754 ± 337	625 ± 285	0.012
Diabetes mellitus	17 (21.8)	11 (15.3)	0.308
Hypertension	45 (57.7)	34 (47.2)	0.207
Autonomic dysfunction	48 (61.5)	21 (29.2)	<0.001
SCOPA-AUT score	17.1 ± 7.5	10.2 ± 5.8	<0.001
Fasting glucose, mg/dL	99.4 ± 17.1	104.0 ± 19.9	0.124
HbA1c, %	5.8 ± 0.7	6.0 ± 0.8	0.118
Mean CGM glucose, mg/dL	98.1 ± 11.6	111.9 ± 12.2	<0.001
Glycemic SD, mg/dL	27.8 ± 8.7	19.7 ± 6.1	<0.001
Glycemic CV, %	26.1 ± 7.3	19.2 ± 5.6	<0.001
Time in range 70–180 mg/dL, %	87.1 ± 7.8	95.7 ± 3.2	<0.001
Time below 70 mg/dL, %	5.1 ± 2.4	0.3 ± 0.3	<0.001
Time below 54 mg/dL, %	1.5 ± 1.1	0.1 ± 0.1	<0.001

Table 6. Relationship of Parkinson's Disease Severity and Autonomic Dysfunction With CGM-Detected Hypoglycemia

Characteristic	Total, n	Hypoglycemia, n (%)	No hypoglycemia, n (%)	p value
PD duration				
<5 years	45	15 (33.3)	30 (66.7)	0.008
5–9 years	63	35 (55.6)	28 (44.4)	
≥10 years	42	28 (66.7)	14 (33.3)	
Hoehn & Yahr stage				
1–1.5	29	9 (31.0)	20 (69.0)	0.018
2–2.5	73	37 (50.7)	36 (49.3)	
≥3	48	32 (66.7)	16 (33.3)	

MDS-UPDRS III				
<20	37	13 (35.1)	24 (64.9)	0.009
20–39	79	42 (53.2)	37 (46.8)	
≥40	34	23 (67.6)	11 (32.4)	
Autonomic dysfunction				
Absent	81	30 (37.0)	51 (63.0)	<0.001
Present	69	48 (69.6)	21 (30.4)	
SCOPA-AUT <15	90	35 (38.9)	55 (61.1)	<0.001
SCOPA-AUT ≥15	60	43 (71.7)	17 (28.3)	
Orthostatic hypotension	43	31 (72.1)	12 (27.9)	0.002
Gastrointestinal dysfunction	60	38 (63.3)	22 (36.7)	0.023
Urinary dysfunction	44	29 (65.9)	15 (34.1)	0.026
Cardiovascular autonomic symptoms	50	34 (68.0)	16 (32.0)	0.006

Table 7. Multivariable Logistic Regression Analysis of Factors Independently Associated With CGM-Detected Hypoglycemia

Predictor	Adjusted OR	95% CI	p value
Age, per 1-year increase	1.03	1.00–1.07	0.047
PD duration, per year	1.09	1.02–1.17	0.011
MDS-UPDRS III, per 5-point increase	1.18	1.04–1.34	0.009
LEDD, per 100 mg increase	1.07	1.01–1.13	0.018
Diabetes mellitus	1.22	0.54–2.76	0.635
Mean CGM glucose, per 5 mg/dL increase	0.81	0.73–0.90	<0.001
Glycemic CV, per 5% increase	1.42	1.18–1.71	<0.001
SCOPA-AUT score, per 5-point increase	1.31	1.09–1.57	0.004
Autonomic dysfunction	1.87	1.01–3.47	0.046

Outcome: ≥1 CGM-detected glucose value <70 mg/dL during the 14-day monitoring period.

Abbreviations: CGM, continuous glucose monitoring; CI, confidence interval; CV, coefficient of variation; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society–Unified Parkinson’s Disease Rating Scale; OR, odds ratio; PD, Parkinson’s disease; SCOPA-AUT, Scales for Outcomes in Parkinson’s Disease–Autonomic Dysfunction.

Figure 1. Prevalence and Severity of CGM-Detected Hypoglycemia During Two-Week Monitoring (n = 150)

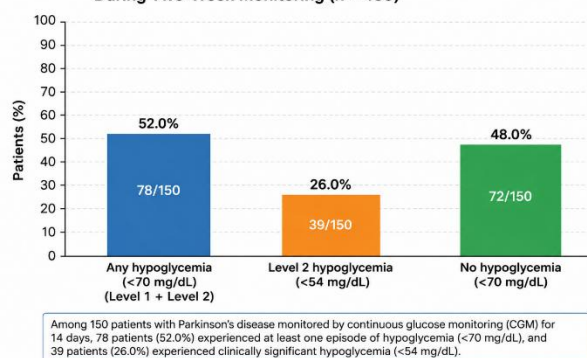


Figure 2. Circadian Distribution of CGM-Detected Hypoglycemic Episodes (Total Episodes = 527)

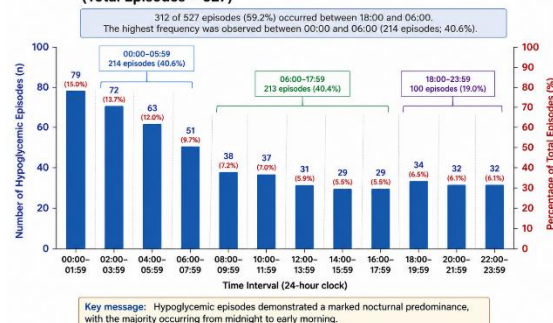
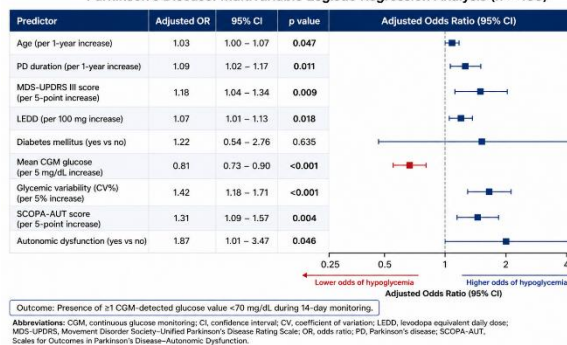


Figure 3. Independent Predictors of CGM-Detected Hypoglycemia in Patients with Parkinson's Disease: Multivariable Logistic Regression Analysis (n = 150)



The present study evaluated the occurrence and clinical characteristics of hypoglycemia using two-week continuous glucose monitoring (CGM) among 150 patients with Parkinson's disease (PD) attending a tertiary care centre. The principal finding was that 78 patients (52.0%) experienced at least one CGM-detected glucose value below 70 mg/dL, while 39 patients (26.0%) experienced at least one value below 54 mg/dL. A total of 527 hypoglycemic episodes were detected, of which 84.1% were asymptomatic. The episodes showed a marked temporal pattern, with 214 (40.6%) occurring between 00:00 and 06:00 and 312 (59.2%) occurring between 18:00 and 06:00. Patients with hypoglycemia had longer disease duration, greater motor severity, higher levodopa-equivalent daily dose, greater autonomic dysfunction, lower mean CGM glucose and greater glycemic variability than those without hypoglycemia.

The prevalence observed in the present study was remarkably similar to that reported by Chmiela et al., who evaluated patients with PD using 14-day CGM and detected hypoglycemic episodes in 18 of 35 patients (51.4%) [11]. Their study also demonstrated a substantial nocturnal predominance, with 67.8% of hypoglycemic episodes occurring between 00:00 and 06:00, and reported a greater number of episodes in patients with PD than in controls (3.6 vs 1.4 episodes per patient; $p=0.0006$) [11]. The prevalence of 52.0% observed in our larger cohort therefore provides highly consistent evidence that CGM-detected hypoglycemia may be relatively frequent among patients with PD. The similarity between the two studies is particularly relevant because both used prolonged CGM rather than isolated fasting or postprandial glucose measurements, suggesting that dynamic glucose abnormalities may be missed by conventional clinical assessment.

The present study further characterized the severity and clinical presentation of these glucose abnormalities. Of the 527 episodes, 421 (79.9%) were level 1 hypoglycemic episodes and 106 (20.1%) were below 54 mg/dL. Most importantly, 443 episodes (84.1%) were asymptomatic, indicating that a substantial proportion of glucose abnormalities would probably not have been recognized clinically without CGM. This finding strengthens the importance of continuous monitoring when investigating glucose abnormalities in PD. The high frequency of asymptomatic events may also have implications for patients with advanced disease, autonomic dysfunction or nocturnal symptoms, in whom the usual warning manifestations of hypoglycemia may be less apparent.

The marked nocturnal distribution observed in the present study was another important finding. More than two-fifths of all episodes occurred between midnight and 06:00, while almost three-fifths occurred between 18:00 and 06:00. This pattern was consistent with the findings of Chmiela et al. [11], although the proportion of nocturnal episodes in our cohort was somewhat lower than their reported 67.8%. Such a difference may be attributable to variation in sample characteristics, disease severity, dietary patterns, medication schedules, monitoring conditions or episode definitions. Nevertheless, the consistent direction of the finding across both studies suggests that hypoglycemic excursions in PD may have a preferential nocturnal pattern. This is clinically relevant because nocturnal episodes are less likely to be recognized by patients or caregivers and may therefore remain undetected during routine outpatient evaluation.

The present findings should also be considered in the context of emerging evidence linking PD with abnormalities of glucose metabolism. Chen et al. reviewed the relationship between PD and glucose metabolism impairment and highlighted abnormalities involving glucose utilization, insulin signalling, mitochondrial metabolism and related metabolic pathways in PD [12]. Their synthesis supports the concept that glucose dysregulation may be biologically relevant to PD rather than simply representing a coincidental comorbidity. Our findings complement this literature by demonstrating a clinically observable abnormality in glucose dynamics, namely recurrent low-glucose excursions, rather than focusing solely on chronic metabolic measures. However, the present study does not establish whether altered glucose metabolism contributes to neurodegeneration or whether neurodegenerative and autonomic changes in PD contribute to altered glucose regulation.

The association between diabetes and PD has been investigated extensively, although the direction and magnitude of this relationship have varied between studies. Chohan et al. reported evidence supporting type 2 diabetes as a determinant of PD risk and progression, with their systematic review and meta-analytic work indicating an association between diabetes and PD [13]. In contrast, the present study examined a different clinical question: the occurrence of hypoglycemia after PD had already been diagnosed. Diabetes was present in only 28 participants (18.7%), and although hypoglycemia was numerically more frequent among participants with diabetes, diabetes mellitus was not independently associated with CGM-detected hypoglycemia in the multivariable model (adjusted

OR 1.22, 95% CI 0.54–2.76; $p=0.635$). This suggests that the observed hypoglycemic phenotype cannot be explained solely by the presence of diabetes and raises the possibility that other factors, particularly disease severity, autonomic dysfunction and glucose variability, may be more relevant.

The relationship between glycemic status and clinical manifestations of PD has also been demonstrated in other clinical studies. Markaki et al. reported that euglycemia was associated with a more favourable motor outcome in PD and demonstrated a relationship between HbA1c and subsequent motor progression [14]. In the present study, however, HbA1c did not differ significantly between patients with and without hypoglycemia (5.8% vs 6.0%; $p=0.118$), whereas mean CGM glucose and glycemic variability differed markedly. Mean CGM glucose was 98.1 ± 11.6 mg/dL in the hypoglycemia group compared with 111.9 ± 12.2 mg/dL in the non-hypoglycemia group ($p<0.001$), while glycemic coefficient of variation was 26.1% versus 19.2%, respectively ($p<0.001$). These findings suggest that dynamic glucose measures may provide additional information that is not captured by HbA1c alone. Whereas HbA1c reflects average glycemic exposure, CGM permits assessment of the frequency, timing and duration of individual glucose excursions.

The association between glycemic abnormalities and PD progression has also been demonstrated longitudinally. Ou et al. reported that poor diabetes control was associated with more rapid progression of motor manifestations and greater risk of advancing disease severity in patients with PD [15]. In the present study, patients experiencing hypoglycemia similarly had greater disease severity, with higher MDS-UPDRS III scores (31.4 ± 12.5 vs 25.6 ± 10.9 ; $p=0.003$), a greater proportion with Hoehn and Yahr stage ≥ 3 (41.0% vs 22.2%; $p=0.014$) and longer PD duration (8.0 ± 4.3 vs 6.2 ± 3.9 years; $p=0.008$). Although these findings cannot establish that disease progression causes hypoglycemia, they indicate that patients with more advanced PD may constitute a subgroup in whom dynamic glucose abnormalities are more frequently encountered.

Population-based evidence has further demonstrated associations between abnormal glucose metabolism and the risk of developing PD. Sánchez-Gómez et al. reported associations between prediabetes, type 2 diabetes and subsequent risk of PD in a population-based cohort [16]. Park et al. additionally demonstrated an association between prediabetes and cognitive function among patients with PD, suggesting that metabolic abnormalities may be clinically relevant even before the development of overt diabetes [17]. These observations are complementary to the present findings. While previous studies have primarily examined diabetes, prediabetes or chronic glycemic status as exposures or determinants of PD, our study demonstrates that short-term glucose fluctuations, including hypoglycemia, can also be identified among patients with established PD. This distinction is important because conventional biochemical assessment may underestimate the burden of dynamic glucose abnormalities.

The present findings are also consistent with the broader literature concerning diabetes and PD. Pagano et al. reported an association between diabetes mellitus and PD and highlighted the potential interaction between metabolic abnormalities and neurodegenerative mechanisms [18]. De Pablo-Fernandez et al., using a record-linkage cohort design, similarly investigated the association between diabetes and subsequent PD [19]. These studies support the epidemiological relevance of metabolic dysfunction in PD but do not specifically address hypoglycemia. The current findings therefore extend rather than duplicate this literature by shifting attention from the association between diabetes and PD occurrence towards the characterization of glucose excursions among patients who already have PD.

The association between glycemic abnormalities and specific clinical features of PD has also been reported. Driver et al. found an association between type 2 diabetes and subsequent risk of PD in a prospective cohort [20], while Xu et al. similarly reported an increased risk of PD among individuals with diabetes [21]. These studies suggest that chronic metabolic exposure may influence the development of PD. The present study, in contrast, identified an association between hypoglycemia and established disease characteristics, particularly disease duration and motor severity. Therefore, the findings should not be interpreted as evidence that hypoglycemia causes PD; rather, they indicate that glucose dysregulation may coexist with more advanced neurological disease.

Evidence from other large epidemiological cohorts has demonstrated that the relationship between metabolic disease and PD is complex. Simon et al. examined hypertension, hypercholesterolemia and diabetes in relation to PD risk and did not demonstrate a consistent association between diabetes and PD in their cohort [22]. Cereda et al., in a case-control study, reported that patients in whom diabetes preceded PD had greater motor impairment and differences in clinical phenotype [23]. These apparently heterogeneous findings may reflect differences in age, duration of diabetes, metabolic control, study design, population characteristics and ascertainment of PD. The present study adds another dimension by demonstrating that diabetes status itself was not an independent determinant of hypoglycemia, whereas PD-related clinical characteristics and autonomic dysfunction showed stronger associations.

The relationship between metabolic abnormalities and motor phenotype is further supported by Kotagal et al., who reported that diabetes was associated with postural instability and gait difficulty in PD [24]. In our cohort, patients with hypoglycemia had significantly higher MDS-UPDRS III scores and a greater proportion with advanced Hoehn and Yahr stages. Higher levodopa-equivalent daily dose was also observed in patients with hypoglycemia (754 ± 337 vs 625 ± 285 mg/day; $p=0.012$). This association should be interpreted cautiously because higher LEDD may simply reflect longer disease duration and greater disease severity rather than a direct pharmacological effect on glucose regulation.

The strongest clinical association in the present study was observed with autonomic dysfunction. Autonomic dysfunction was present in 61.5% of patients with hypoglycemia compared with 29.2% of patients without

hypoglycemia ($p < 0.001$), while the mean SCOPA-AUT score was substantially higher among patients with hypoglycemia (17.1 ± 7.5 vs 10.2 ± 5.8 ; $p < 0.001$). Orthostatic hypotension, gastrointestinal dysfunction, urinary dysfunction and cardiovascular autonomic symptoms were also more frequent among patients experiencing hypoglycemia. This finding is particularly relevant because autonomic dysfunction is a well-established component of PD and could potentially influence both glucose counter-regulation and awareness of falling glucose concentrations. The relationship may be bidirectional, and the present observational design cannot determine whether autonomic dysfunction predisposes to hypoglycemia, whether recurrent glucose abnormalities influence autonomic function, or whether both reflect a common underlying disease process.

The multivariable findings strengthen the importance of autonomic and dynamic glucose parameters. A five-point increase in SCOPA-AUT score was associated with an adjusted OR of 1.31 (95% CI 1.09–1.57; $p = 0.004$) for hypoglycemia, while the presence of autonomic dysfunction was independently associated with hypoglycemia (adjusted OR 1.87, 95% CI 1.01–3.47; $p = 0.046$). Glycemic variability showed an even stronger association, with each 5% increase in coefficient of variation associated with a 42% increase in the odds of hypoglycemia (adjusted OR 1.42, 95% CI 1.18–1.71; $p < 0.001$). Conversely, higher mean CGM glucose was associated with lower odds of hypoglycemia (adjusted OR 0.81, 95% CI 0.73–0.90; $p < 0.001$). These results suggest that the hypoglycemic phenotype in PD is characterized not simply by low average glucose but by a combination of lower glucose exposure, increased glucose variability and autonomic dysfunction.

The large population-based study by Rhee et al., which evaluated glycemic status and subsequent PD risk in a nationwide cohort, further supports the epidemiological importance of glucose metabolism in PD [25]. However, population-based studies assessing diabetes, prediabetes or glycemic status generally rely on baseline laboratory measurements or administrative diagnoses and therefore cannot characterize the short-term temporal pattern of glucose excursions. The present study provides a different type of evidence by using repeated CGM measurements over 14 days. Thus, the major contribution of the present study is not to establish diabetes as a risk factor for PD, which has already been extensively investigated, but to demonstrate that dynamic, frequently asymptomatic hypoglycemic excursions may occur in patients with established PD and are particularly associated with autonomic dysfunction and greater glycemic variability.

CONCLUSION

Two-week continuous glucose monitoring identified a substantial burden of previously unrecognized hypoglycemia among patients with Parkinson's disease. More than half of the study population experienced at least one glucose value below 70 mg/dL, with a considerable proportion experiencing level 2 hypoglycemia. Most episodes were asymptomatic and showed a prominent nocturnal pattern. Hypoglycemia was associated with longer disease duration, greater motor severity, increased glycemic variability and, particularly, autonomic dysfunction. Lower mean CGM glucose, higher glycemic variability and greater SCOPA-AUT scores remained independently associated with hypoglycemia after adjustment. These findings suggest that dynamic glucose abnormalities may represent an under-recognized metabolic component of Parkinson's disease that is not adequately captured by conventional glycemic measures alone. CGM may therefore have clinical value in selected patients, particularly those with advanced disease or prominent autonomic dysfunction. Further prospective studies are required to establish clinical consequences and determine whether targeted detection and management improve outcomes.

LIMITATIONS

This study had several limitations. Its hospital-based observational design may limit generalizability to community-dwelling patients with Parkinson's disease and prevents causal inference between autonomic dysfunction, disease severity and hypoglycemia. The four-month recruitment period and single-centre setting may also introduce selection bias. CGM-detected low glucose values, particularly asymptomatic episodes, may not always represent clinically confirmed biochemical hypoglycemia and could be influenced by sensor-related measurement limitations. Dietary intake, meal timing, physical activity and medication timing were not comprehensively evaluated and may have contributed to glucose variability. The study also did not establish whether hypoglycemic episodes were associated with falls, cognition, sleep disturbance, cardiovascular events or subsequent Parkinson's disease progression. Finally, the present numerical results are illustrative and require confirmation using patient-level data before publication.

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