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Progression of postural control and gait deficits in Parkinson's disease and freezing of gait: A longitudinal study

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ABSTRACT

Background and aims: The relationship between impaired postural control and freezing of gait (FOG) in Parkinson's disease (PD) is still unclear. Our aim was to identify if postural control deficits and gait dysfunction progress differently in freezers compared to non-freezers and whether this relates to FOG development.

Methods: 76 PD patients, classified as freezer (n = 17) or non-freezer (n = 59), and 24 controls underwent a gait and postural control assessments at baseline and after 12 months follow-up. Non-freezers who developed FOG during the study period were categorized as FOG converters (n = 5). Gait was analyzed during walking at self-preferred pace. Postural control was assessed using the Mini-BESTest and its sub-categories: sensory orientation, anticipatory, reactive and dynamic postural control.

Results: Mini-BESTest scores were lower in PD compared to controls ($p < 0.001$), and in freezers compared to non-freezers ($p = 0.02$). PD has worse anticipatory ($p = 0.01$), reactive ($p = 0.02$) and dynamic postural control ($p = 0.003$) compared to controls. Freezers scored lower on dynamic postural control compared to non-freezers ($p = 0.02$). There were no baseline differences between converters and non-converters. Decline in postural control was worse in PD compared to controls ($p = 0.02$) as shown by a greater decrease in the total Mini-BESTest score. Similar patterns were found in freezers ($p = 0.006$), who also showed more decline in anticipatory ($p < 0.001$) and dynamic postural control ($p = 0.02$) compared to non-freezers. FOG converters had a greater decline in the total Mini-BESTest ($p = 0.005$) and dynamic postural control scores ($p = 0.04$) compared to non-converters. Gait outcomes showed no significant differences in any of the analyses.

Conclusion: FOG is associated with more severe decline in postural control, which can be detected by the clinical Mini-BESTest.

1. Introduction

Impaired postural control and gait are important contributors to reduced mobility in patients with Parkinson's disease (PD) [1]. Postural control dysfunction impacts on quality of life in PD as it is one of the major causes of increased fall risk [2]. Recurrent falls are an even larger concern in patients with freezing of gait (FOG) [2,3]. FOG is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk [4]. Although several studies have suggested that impaired postural control and falls are two related phenomena (for review: [2]), the relationship between postural control and FOG is currently still unclear.

Postural control requires several mechanisms to align the body with respect to gravity, the support surface and visual surroundings and is aimed to stabilize the COM of the body relative to its base of support [1]. According to a recently proposed multi-component framework, these control systems comprise postural sway during sensory manipulations in quiet stance, reactive postural control,

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anticipatory postural adjustments (APAs) and dynamic balance [1]. These mechanisms have been investigated in PD in general, but studies in the context of FOG are scarce and showed contradictory results. Two of these studies found altered postural sway parameters indicating a lower adaptability of postural sway in freezers compared to non-freezers [5,6]. A recent study from Schlenstedt et al. (2015) showed a posterior shift in the center of pressure in freezers compared to non-freezers, which was hypothesized to generate inadequate forward movement progression during gait initiation, thereby contributing to FOG [7]. However, the same study found no alterations in sway properties of the center of pressure, corroborating our earlier findings of comparable sway parameters in freezers and non-freezers, even when sensory input was compromised [8]. We also examined APAs during a voluntary weight-shifting paradigm demonstrating poorer directional control in freezers compared to non-freezers. Deficient APA's have been consistently reported in freezers [9–11] and are suggested to have a close relationship to FOG due to the observation that knee trembling prior to a freezing episode represents decoupling between APAs and the selection of the appropriate motor program at gait initiation [10]. Moreover, high-frequency knee trembling is currently used to identify freezing episodes [12].

Although these studies provided insights into some of the important individual components of freezing-related postural instability, to date, there is no consensus on which aspects of this multicomponent process are most affected in FOG. Previous studies investigated this matter in a cross-sectional manner, making it difficult to pinpoint specific mechanism contributing to FOG. Therefore, the current study applied an integrated and longitudinal approach to clarify whether and how different postural control aspects underpin FOG. The Mini-BESTest is a clinical test, which includes sub-scores of anticipatory and reactive postural control, sensory orientation and dynamic postural control. It was recently shown to be able to detect balance decline in PD after 6 and 12 months follow-up [13] and was indicated by a recent study from Duncan et al. (2015) [14] to be the preferred tool for clinically assessing postural control deficits associated with FOG in mild to moderate PD. The same research group also demonstrated the Mini-BESTest to be a more sensitive predictor of falls in PD (sensitivity = 0.75; specificity = 0.79) in comparison with gait speed (sensitivity = 0.67; specificity = 0.72) [15]. Although previous studies suggested that gait impairment is already present in de novo and early PD [16], a recent progression study could only detect subtle changes in gait speed, step length and swing time after 18 months follow-up in PD compared to controls [17].

Therefore, this study aimed to evaluate if decline in postural control and gait performance are related to FOG and its development. For this purpose, we compared Mini-BESTest scores between freezers and non-freezers cross-sectionally and investigated the progression after 12 months follow-up. In addition, we examined the relationship with the development of FOG by comparing the same outcome measures in non-freezers who converted to freezers during the follow-up period with those who did not. We also investigated the sub-scores of the Mini-BESTest to identify which aspects of postural control dysfunction were most FOG-related.

2. Methods

2.1. Subjects

Seventy-six PD patients and 24 healthy age-matched controls were recruited for this study (for details, see Supplementary Materials). Patients were included if they were diagnosed with PD according to the UK Brain bank criteria and if they had a Hoehn and Yahr (H&Y) stage between 1 and 3 while 'off' medication. Exclusion criteria were a Mini-Mental State Examination (MMSE) score < 24 and presence of neurological comorbidities. The New freezing of gait questionnaire (NFOG-Q) or FOG occurrence in the lab was used to classify patients as freezers (FOG) (n = 17) or non-freezers (NFOG) (n = 59). Disease severity was measured by Movement Disorder Society Unified Parkinson's Disease Rating Scale III (MDS-UPDRS) and H&Y staging while 'off' medication. Disease duration was expressed as the number of years since onset of the first motor symptom. The study was approved by the local ethics committee of the University Hospitals Leuven and all subjects gave written informed consent prior to participation.

2.2. Test protocol

Subjects underwent a postural control and gait assessment at baseline and after 12 months follow-up. All tests were performed in the practically defined 'off' state. Five PD patients and 4 controls only underwent baseline assessment because they were recruited as part of another cross-sectional study which included the same balance assessments. In addition, 4 PD patients dropped out during the follow-up period due to personal reasons or development of comorbidity. This led to a final sample size of 67 PD patients (11 FOG and 56 NFOG) and 20 controls for the longitudinal analysis.

2.3. Postural control assessment

Postural control was assessed using the mini-BESTest [18], which is derived from the BESTest. It consists of 14 items with scores ranging between 0 and 2. The anticipatory postural control part (part 1: 3 items) it tests the ability to prepare for voluntary center of mass (COM) movements. The reactive postural control (part: 3 items) probes the involuntary postural responses when postural support is suddenly withdrawn. The sensory orientation sub-score assesses postural control when sensory information is compromised (part 3: 3 items). Finally, dynamic postural control tests CoM stability in challenging gait conditions such as speed changes and dual-tasking (part 4: 5 items). Outcome measures were scores of the 4 sub-domains and the total score ranging between 0 and 28. In addition, we collected fall data via fall diaries [19] during the 12 month follow-up period. Subjects were contacted monthly to go over their fall history. If one or more falls occurred during this 12 month follow-up, participants were considered to be fallers. One patient and 4 healthy controls did not fill-out their diaries regularly and were excluded from the falls data analysis.

2.4. Gait assessment

Gait analysis was performed using the VICON 3D motion analysis system (©Vicon Motion Systems Ltd.; Oxford Metrics, UK) as previously described [20]. Gait speed, swing time and step length were chosen as outcomes as they were recently shown to be significantly declined after 18 month follow-up in the context of the 'Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation–Parkinson Disease' (ICICLE-PD) study [17]. We also included variability measures of swing time and step length as they proved important markers of FOG [21] and falling [22].

2.5. Statistical analyses

Descriptive statistics were compared between groups using unpaired T-tests for continuous variables and chi-squared tests for non-continuous variables. Paired T-tests were used to evaluate within group differences in PD and controls between baseline follow-up. Outcome measures for the baseline postural control and

gait assessment were compared between PD patients and healthy controls using independent T-tests or Mann-Whitney *U* tests depending on the distribution of the variables. To compare freezers with non-freezers, we used ANCOVA analyses to compare spatiotemporal gait outcomes and total mini-BESTest scores. To account for differences in group characteristics, we added age and MDS-UPDRS III as covariates. Although H&Y, disease duration and LED were also significantly different between freezers and non-freezers, we did not control for them as tests were performed 'off' medication and these disease characteristics significantly correlated with MDS-UPDRS III scores. The abnormally distributed mini-BESTest sub-scores were compared between freezers and non-freezers using Mann-Whitney *U* tests. If they correlated significantly with age or MDS-UPDRS III, analyses were repeated in a subgroup of non-freezers that was matched with the freezer group to corroborate the earlier findings (see Supplementary Materials). In addition, we performed an analysis with regard to FOG conversion using Mann-Whitney *U* tests. Here, a distinction was made between non-freezers who converted to freezers during follow-up (CONV) ($n = 5$) and those who did not (NCONV) ($n = 52$). Based on information from the DATATOP study [23], we a priori expected to find between 15 and 20% of conversion. However actual conversion rates were lower (8.5%).

Progression was assessed by the proportional change between baseline and 12 months for each outcome measure. These change scores were compared between PD and controls and between CONV and NCONV using unpaired T-tests or Mann-Whitney *U* tests depending on the distribution. Comparison between FOG and NFOG was performed using similar criteria as for the baseline measures. We performed Holms-Bonferroni corrections [24]for multiple comparison on each group of comparison (baseline postural control, baseline gait, postural control decline and gait decline). Both the corrected and uncorrected p-values were reported.

Finally, we also examined Spearman correlations between postural control-related proportional decline and increased MDS-UPDRS III, LED and fall frequencies in the entire patient group. α was set at 0.05. We conducted a post-hoc power analysis based on previous information on mini-BESTest scores in patients with FOG [14] and decline in Mini-BESTest scores after 12 months follow-up [13]. Sample sizes were calculated for detecting baseline differences and progression in postural control decline (G*Power 3.1.9.2). These analyses indicated required sample sizes of 17 patients with FOG and 59 patients without FOG to detect baseline differences in total Mini-BESTest scores at a power of 0.8 and α-level of 0.05. At the same conditions, the required sample size to detect progression in postural control decline was 3. For secondary outcome measures a power analysis was performed, the results of which are reported in the Supplementary Materials.

3. Results

3.1. Subject characteristics

Baseline subject characteristics are shown in Table 1. PD patients were age- and gender-matched compared to controls. PD had lower MMSE-scores compared to controls and had a higher fall frequency. A sub-analysis within the PD group showed that freezers were older, had longer disease duration and worse disease severity compared to non-freezers. In addition, the male/female ratio as well as the frequency of fallers was larger in freezers compared to non-freezers. Within the non-freezer group, no differences were found between those who developed FOG within 12 months and those who did not.

Proportional decline in subject characteristics is shown in Table 1. In PD patients, MDS-UPDRS III scores significantly increased with 19% or 3.1 points over 12 months and NFOG-Q scores increased with 9% or 0.8 points. Additionally, LED significantly increased with 33.9% or 77.4 mg/day. None of subject characteristics progressed differently between PD and controls, nor between FOG and NFOG or between CONV and NCONV.

3.2. Baseline assessment

At baseline, postural control was significantly more affected in PD compared to controls (Table 2), indicated by worse performance on the total mini-BESTest ($p < 0.001$) and the sub-scores for anticipatory ($p = 0.01$), reactive ($p = 0.02$) and dynamic postural control ($p = 0.003$). There were no differences in spatiotemporal gait variables between PD and controls.

Freezers showed similar postural control impairment compared to non-freezers as shown by lower total Mini-BESTest scores ($p = 0.02$), as well as lower scores on the sub-items for anticipatory ($p < 0.001$), reactive ($p = 0.008$) and dynamic postural control ($p < 0.001$) (Table 2). The same results were found when p-values were corrected for multiple testing. However, all subs-scores were correlated with MDS-UPDRS III (anticipatory postural control: rho $= -0.43$, $p < 0.001$; reactive postural control: rho $= -0.35$, $p = 0.002$; sensory orientation: rho $= -0.36$, $p = 0.001$; dynamic postural control: rho $= -0.46$, $p < 0.001$) and anticipatory, reactive and dynamic postural control (anticipatory: rho $= -0.61$, $p < 0.001$; reactive: rho $= -0.39$, $p < 0.001$; dynamic: rho $= -0.47$, $p < 0.001$) were correlated with age. Therefore, we repeated the analysis in smaller groups matched for age and disease severity (Supplementary Materials). The results showed that freezers had worse dynamic postural control compared to non-freezers ($p = 0.02$). Freezers and non-freezers were not different with regard to their gait outcomes.

3.3. 12 month follow-up

PD patients did not show an altered decline in postural control or gait measures except for a larger decrease in total Mini-BESTest scores compared to controls ($p = 0.02$) (Table 3). However, this result was not retained after multiple testing corrections. Similarly, we found a larger decline in the total Mini-BESTest scores in FOG compared to NFOG ($p = 0.006$) as well as in the sub-items on anticipatory ($p < 0.001$) and dynamic postural control ($p = 0.02$), the latter of which was not retained after multiple testing corrections. The same analysis in the smaller matched subgroups led to similar results (Table S1). There were no differences in the pattern of results of spatiotemporal gait outcomes between FOG and NFOG.

3.4. FOG conversion

Baseline assessment could not reveal any significant differences between patients who converted to 'freezers' during 12 months follow-up and those who did not (Table 4). In contrast, converters showed a significantly greater decline in total mini-BESTest scores ($p = 0.005$) as well as in the sub-score evaluating dynamic postural control ($p = 0.04$), but the latter was not retained after multiple testing corrections. There was no different decrease in spatiotemporal gait outcomes between CONV and NCONV.

3.5. Correlations

None of the postural control-related proportional decline scores were correlated to the increase in MDS-UPDRS III, LED and fall frequencies. The decline in MDS-UPDRS III (rho $= 0.26$; $p = 0.04$)

Table 1
Baseline subject characteristics and progression after 12 months follow-up.

	PD (n = 76)	HC (n = 24)	p-Value	FOG (n = 17)	NFOG (n = 59)	p-Value	NCONV (n = 52)	CONV (n = 5)	p-Value
Baseline									
Age (years)	60.6 (±10.0)	59.9 (±9.6)	0.76	67.4 (±9.3)	58.6 (±9.4)	<0.05	59.1 (±9.2)	58.8 (±10.7)	0.95
Sex (M/F)	47/29	15/9	0.95	16/1	31/28	<0.05	28/24	3/2	0.79
Disease Duration (years)	6.8 (±4.6)	NA	NA	10.1 (±6.3)	5.8 (±3.4)	<0.05	5.7 (±3.4)	7.8 (±3.3)	0.25
MDS-UPDRS III (0–132)	27.4 (±12.3)	NA	NA	38.9 (±11.5)	25.3 (±11.3)	<0.05	25.3 (±11.3)	30.8 (±7.6)	0.29
H&Y (1–5)	2.1 (±0.5)	NA	NA	2.4 (±0.5)	2.0 (±0.6)	<0.05	2.0 (±0.6)	2.0 (±0.0)	0.94
LED (mg/day)	463.2 (±277.7)	NA	NA	608.4 (±271.0)	415.6 (±255.7)	<0.05	422.3 (±254.8)	460.0 (±276.2)	0.76
NFOG-Q (0–29)	3.5 (±7.1)	NA	NA	17 (±5.0)	NA	NA	NA	NA	NA
MMSE (0–30)	28.4 (±1.5)	29.4 (±0.8)	<0.05	28.0 (±1.3)	28.5 (±1.6)	0.31	28.5 (±1.5)	27.6 (±2.1)	0.21
Fall frequency (12 months)	1.2 (±2.4)	0.0 (±0.0)	<0.05	2.1 (±2.7)	1.0 (±2.3)	0.15	1.0 (±2.4)	0.4 (±0.5)	0.55
Percentage of fallers (%)	38.2	0.0	<0.05	58.3	33.9	<0.05	33.3	40.0	1.00
Progression									
MDS-UPDRS III (%)	19.0 (±38.6)*	NA	NA	19.5 (±36.1)	18.9 (±39.4)	0.96	19.0 (±40.5)	17.5 (±19.6)	0.66
H&Y (%)	9.1 (±33.8)	NA	NA	4.2 (±14.4)	10.1 (±36.6)	0.36	11.1 (±38.2)	0.0 (±0.0)	0.78
LED (%)	33.9 (±72.3)*	NA	NA	39.2 (±80.2)	32.7 (±71.3)	0.79	32.9 (±73.5)	30.9 (±43.6)	0.36
NFOG-Q (%)	9.0 (±40.3)*	NA	NA	9.0 (±40.3)	NA	NA	NA	NA	NA
MMSE (%)	0.0 (±6.2)	0.0 (±3.4)	1.0	0.7 (±4.6)	−0.1 (±6.5)	0.66	−0.3 (±6.7)	1.5 (±5.0)	0.50

Means and standard deviations (SD) at baseline and for proportional decline are reported. Positive values for the decline parameters indicate increases over time and negative values indicate decreased over time. * Indicates significant ($p < 0.05$) within-group changes between baseline and 12 months follow-up. CONV: Conversion to freezing of gait; FOG: Freezing of Gait; H&Y: Hoehn and Yahr; HC: Healthy controls; LED: Levodopa Equivalent Dose; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE: Mini-Mental State Examination; NA: Not Applicable; NCONV: No conversion to freezing of gait; NFOG: No Freezing of Gait; PD: Parkinson's Disease; NFOG-Q: New Freezing of Gait Questionnaire.

Table 2
Baseline postural control and gait assessment.

	PD	HC	p-Value	Corrected p-value	FOG	NFOG	p-value	Corrected p-value
Postural control								
Mini-BESTest total (0–28)	23.3 (±4.0)	26.0 (±1.8)	**<0.001**	**<0.001**	19.4 (±4.5)	24.4 (±3.0)	**0.02**§	**0.03**
Anticipatory postural control (0–6)	4.6 (±1.4)	5.4 (±0.8)	**0.01**	**0.03**	3.4 (±1.6)	5.0 (±1.0)	**<0.001**	**0.001**
Reactive postural control (0–6)	4.3 (±1.6)	5.2 (±0.9)	**0.02**	**0.04**	3.3 (±1.8)	4.6 (±1.5)	**0.008**	**0.02**
Sensory orientation (0–6)	5.8 (±0.5)	5.9 (±0.4)	0.13	0.13	5.6 (±0.7)	5.8 (±0.5)	0.12	0.12
Dynamic postural control (0–10)	8.6 (±1.5)	9.5 (±0.6)	**0.003**	**0.01**	7.1 (±1.7)	9.0 (±1.1)	**<0.001**	**0.001**
Gait								
Step length (mm)	550.6 (54.0)	565.4 (±29.8)	0.24	1.00	527.3 (±63.9)	555.4 (±51.1)	0.28§	0.84
Swing time (s)	0.45 (±0.02)	0.46 (±0.01)	0.26	1.00	0.45 (±0.01)	0.45 (±0.02)	0.73§	1.00
Gait speed (m/s)	1.00 (±0.12)	1.03 (±0.09)	0.31	1.00	0.97 (±0.16)	1.01 (±0.10)	0.70§	1.00
Step length variability (%)	13.7 (±5.8)	13.6 (±4.8)	0.93	1.00	15.6 (±4.3)	13.3 (±6.0)	0.18§	0.72
Swing time variability (%)	9.2 (±3.7)	9.6 (±3.5)	0.73	1.00	10.6 (±3.2)	9.0 (±3.7)	0.12§	0.60

Means and standard deviations are reported. § Indicates analyses that were corrected for age and MDS-UPDRS III scores. P-values below the alpha-level of significance are indicated in bold. FOG: Freezing of Gait; HC: Healthy controls; NFOG: No Freezing of Gait; PD: Parkinson's Disease.

Table 3
Progression in postural control and gait over 12 months.

	PD	HC	p-Value	Corrected p-value	FOG	NFOG	p-Value	Corrected p-value
Postural control								
Mini-BESTest total (%)	−6.9 (±16.3)	−1.0 (±6.6)	**0.02**	0.10	−20.9 (±27.0)	−3.9 (±11.2)	**0.006**§	**0.02**
Anticipatory postural control (%)	−10.3 (±24.9)	−2.6 (±15.5)	0.09	0.36	−34.7 (±28.0)	−5.1 (±20.9)	**<0.001**	**<0.001**
Reactive postural control (%)	−0.1 (±45.0)	1.4 (±24.6)	0.74	0.74	−14.4 (±68.9)	3.0 (±38.2)	0.18	0.36
Sensory orientation (%)	−4.0 (±20.5)	1.3 (±5.6)	0.22	0.60	−9.2 (±31.1)	−2.9 (±15.1)	0.62	0.62
Dynamic postural control (%)	−4.8 (±20.5)	−0.4 (±6.5)	0.20	0.60	−13.9 (±38.8)	−2.9 (±13.8)	**0.02**	0.06
Gait								
Step length (%)	−3.1 (±16.5)	−4.0 (±7.8)	0.81	1.00	−5.7 (±33.7)	−2.5 (±10.5)	0.98§	1.00
Swing time (%)	−0.4 (±5.8)	0.41 (±5.6)	0.61	1.00	−1.7 (±6.1)	−0.1 (±5.8)	0.57§	1.00
Gait speed (%)	−7.3 (±23.1)	−8.0 (±12.0)	0.90	1.00	−10.6 (±45.4)	−6.6 (±15.7)	0.92§	1.00
Step length variability (%)	52.3 (±180.9)	42.7 (±153.8)	0.98	1.00	23.2 (±74.6)	58.3 (±195.8)	0.80§	1.00
Swing time variability (%)	9.8 (±85.3)	5.9 (±108.5)	0.28	1.00	−0.1 (±62.8)	11.9 (±89.6)	0.72§	1.00

Means and standard deviations are reported for the proportional decline parameters. Positive values indicate increases over time and negative values indicate decreased over time. § Indicates analyses that were corrected for age and MDS-UPDRS III scores. P-values below the alpha-level of significance are indicated in bold. FOG: Freezing of Gait; HC: Healthy controls; NFOG: No Freezing of Gait; PD: Parkinson's Disease.

was related to decline in both step length (rho = 0.26; p = 0.04) and gait speed (rho = 0.29; p = 0.02). Deterioration of postural control parameters was not associated with increased MDS-UPDRS III and LED values.

4. Discussion

The purpose of this study was to evaluate deterioration in postural control in patients with PD with and without FOG. We used the clinical Mini-BESTest to assess baseline characteristics as

Table 4
Baseline characteristics and progression in postural control and gait related to FOG conversion.

	Baseline				12 month progression			
	CONV	NCONV	p-Value	Corrected p-value	CONV	NCONV	p-Value	Corrected p-value
Postural control								
Mini-BESTest total	24.8 (±1.6)	24.3 (±3.1)	0.97	1.00	−16.3 (±6.9)	−2.7 (±10.9)	**0.005**	**0.03**
Anticipatory postural control	4.8 (±1.3)	5.0 (±1.0)	0.73	1.00	−15.0 (±14.9)	−4.1 (±21.3)	0.27	0.54
Reactive postural control	5.6 (±0.5)	4.4 (±1.5)	0.11	0.44	−16.0 (±34.2)	4.9 (±38.3)	0.37	0.54
Sensory orientation	6.0 (±0.0)	5.8 (±0.5)	0.59	1.00	−13.3 (±13.9)	−1.8 (±15.0)	**0.07**	0.21
Dynamic postural control	8.4 (±0.5)	9.0 (±1.2)	0.08	0.44	−18.3 (±20.8)	−1.4 (±12.1)	**0.04**	0.16
Gait								
Step length	546.0 (±4.4)	556.3 (±54.3)	0.45	1.00	−5.3 (±6.3)	−2.3 (±10.9)	0.58	1.00
Swing time	0.45 (±0.01)	0.45 (±0.02)	0.84	1.00	−2.4 (±4.2)	0.2 (±5.9)	0.23	0.92
Gait speed	1.00 (±0.06)	1.01 (±0.11)	0.42	1.00	−9.2 (±14.2)	−6.3 (±16.0)	0.63	1.00
Step length variability	14.3 (±5.2)	13.2 (±6.3)	0.84	1.00	3.2 (±95.6)	64.1 (±203.2)	0.41	1.00
Swing time variability	10.4 (±3.1)	8.8 (±3.8)	0.24	1.00	−31.0 (±50.6)	16.4 (±92.0)	0.11	0.55

Means and standard deviations are reported. For the baseline characteristics CoP amplitude is expressed in mm, CoP velocity is expressed in mm/s, step length is expressed in mm, swing time is expressed in s and gait speed is expressed in m/s. All progression parameters and the gait variability measures are expressed in percentages. Positive values indicate increases over time and negative values indicate decreased over time. P-values below the alpha-level of significance are indicated in bold. FOG: Freezing of Gait; HC: Healthy controls; NFOG: No Freezing of Gait; PD: Parkinson's Disease.

well as the proportional decline over 12 months. By combining this with an assessment of the progression of gait and controlling for disease confounding factors, we were able to identify 6 determinants of FOG, i.e. 1) total Mini-BESTest score; 2) anticipatory postural control; 3) reactive postural control; 4) dynamic postural control; 5) decline in the total Mini-BESTest score and 6) decline in anticipatory postural control. Moreover, our exploratory investigation of FOG conversion allowed us to pinpoint key factors of FOG emergence, i.e. decline in general postural control as indicated by worse total Mini-BESTest scores.

4.1. Baseline assessment

The cross-sectional results showed worse postural control in PD compared to controls, which was detected by the total Mini-BESTest score as well as its sub-scores. This specifically indicated that altered anticipatory, reactive and dynamic postural control distinguished between PD and controls, confirming the results of previous cross-sectional studies [25,26]. Uncorrected analyses showed that the same postural control systems were more severely affected in freezers compared to non-freezers. However, after correcting for age and disease severity differences between groups, only dynamic postural control and the total Mini-BESTest score retained significance. This suggests that either statistical power decreased due to smaller sample sizes in the matched patient subgroups or that motor progression or ageing explained large parts of the variability in anticipatory and reactive balance. The latter explanation is unlikely for anticipatory postural control, as longitudinally, this mini-BESTest item showed greater proportional decline in freezers compared to non-freezer independent of disease severity. In addition, there was no correlation between decline in anticipatory postural control and changes in MDS-UPDRS III scores after 12 months follow-up. Faulty coupling between anticipatory preparation of stepping and the motor program to initiate the stepping movement was previously suggested to contribute to FOG [10] and induced high frequency knee trembling during a FOG-episode [11].

4.2. 12 month follow-up

In line with the cross-sectional results, the longitudinal analyses showed that the Mini-BESTest was strikingly sensitive to postural control deterioration over a period of one year. Not only did PD patients have a greater decline in total Mini-BESTest scores than controls, this pattern was also present in freezers compared to non-freezers. While consensus is lacking about the use of laboratory-based postural control measures to distinguish between freezers and non-freezers [8,10], the Mini-BESTest was shown to be sensitive to postural control impairment related to FOG [14] as well as to postural control deterioration in PD in general over a period of 2 years [13]. Our results add to this knowledge that the total Mini-BESTest score and the sub-items for anticipatory and dynamic postural control were differentially affected in freezers and non-freezers with time. In contrast to a previous longitudinal study in PD [13], freezers had an average decline of 4.75 points on the Mini-BESTest, which exceeded the minimal detectable change of 3.5 points, thus suggesting that the balance deterioration was clinically relevant [27]. Similar to a recent 18-month follow-up study [17], the present results showed increased MDS-UPDRS III scores and LED over 12 months. The proportional decline in MDS-UPDRS III and baseline MMSE-scores were, however, not correlated with balance decline, suggesting that this is an isolated problem that emerges independently from motor progression.

The current findings suggest that dynamic postural control was particularly important for FOG and reiterated previous work by Duncan et al. [17]. The dynamic balance sub-score of the Mini-BESTest includes the assessment of stability during turning, obstacle avoidance, gait initiation and dual-tasking. These aspects of gait adaptation have also repeatedly shown to elicit abnormal gait kinematics in patients with FOG [11,28,29]. Given the intricate linkage between gait and balance, full separation of dynamic balance from locomotor control mechanisms is therefore not feasible or correct.

4.3. FOG conversion

The significance of worsening of postural control was additionally highlighted by its relation to FOG conversion. Our results indicated that converters had greater proportional decline in total mini-BESTest scores as well as in anticipatory postural control. Although these results were obtained in a small group of patients, they suggest that specific postural control components may contribute to the development of FOG. The fact that these changes were independent of motor progression, underscores the possibility that a specific pathophysiological mechanisms underlies both impaired postural control and FOG. Although this hypothesis was previously put forward and supported by several studies [3,4], recent work from Nonnekes et al. contradicted this notion [30].

They reported that hypometric balance correcting responses (during reactive postural control tasks) were specific to patients with postural instability. In contrast, the absence of acceleration in postural response latencies after a startling acoustic stimulus, the so-called StartReact paradigm, proved specific to freezers [30]. Start-react responses are thought to probe the reticulospinal network, indicating that integrity changes of at least part of the reticulospinal system are involved in FOG and not in balance control. However, it could also be that this study probed components of postural control which were less specific to FOG. This stresses the need to consider the different aspects of postural control separately in studies addressing the pathophysiology of FOG.

The absence of impaired gait kinematics between the subgroups with and without FOG in both the baseline and the 12 month follow-up analyses was striking. However, other studies reported global impairment in all 5 gait domains in de novo PD patients partly 'on' medication [17] as well as in freezers compared to non-freezers [31,32]. The present correlation analyses showed that decline in gait quality was weakly related to more severe motor progression. As we corrected all analyses for disease severity with respect to FOG, this may have obscured the presence of gait abnormalities. Dissimilarities with the outcomes of a previous longitudinal study [17] could be due to medication state, shorter follow-up times, patient characteristics or statistical power differences.

4.4. Limitations

The small sample size of FOG converters was a limitation of the current study. Although post-hoc sample size calculation indicated the current sample sizes were sufficient to detect decline in general postural control, it should be noted that the current results may not have properly detected deterioration in the different components of postural control. Future studies should aim to include larger numbers of non-freezing PD patients and prolong follow-up time to increase conversion rates.

4.5. Conclusion

In conclusion, the most important and novel result of this study was that PD patients with FOG showed more severe progression in abnormalities of postural control when compared to their non-freezing counterparts, while no differential decline of the gait pattern was present. These results are clinically relevant as progression of postural instability was detected by the Mini-BESTest, a test that can be administered in a clinical context in less than 15 min. In addition, the total Mini-BESTest score deteriorated more severely in non-freezing PD patients who developed FOG during the follow-up period compared to those who did not. This suggests that impaired postural control and FOG may at least partially share underlying mechanisms.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.04.029.

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