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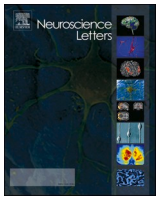

Effect of freezing of gait and dopaminergic medication in the biomechanics of lower limbs in the gait of patients with Parkinson's disease compared to neurologically healthy

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ABSTRACT

Introduction: This study aims to evaluate the effects of medication, and the freezing of gait (FoG) on the kinematic and kinetic parameters of gait in people with Parkinson's disease (pwPD) compared to neurologically healthy.
Methods: Twenty-two people with a clinical diagnosis of idiopathic PD in ON and OFF medication (11 FoG), and 18 healthy participants (control) were selected from two open data sets. All participants walked on the floor on a 10-meter-long walkway. The joint kinematic and ground reaction forces (GRF) variables of gait and the clinical characteristics were compared: (1) PD with FoG (pwFoG) and PD without FoG (pwoFoG) in the ON condition and control; (2) PD with FoG and PD without FoG in the OFF condition and control; (3) Group (PD with FoG and PD without FoG) and Medication.
Results: (1) FoG mainly affects distal joints, such as the ankle and knee; (2) PD ON showed changes in the range of motion of both distal and proximal joints, which may explain the increase in step length and gait speed expected with the use of L-Dopa; and (3) the medication showed improvements in the kinematic and kinetic parameters of the gait of people with pwFoG and pwoFoG equally; (4) pwPD showed a smaller second peak of the vertical component of the GRF than the control.
Conclusion: The presence of FoG mainly affects distal joints, such as the ankle and knee. PD presents a lower application of GRF during the impulse period than healthy people, causing lower gait performances.

1. Introduction

The gait of people with Parkinson's disease (pwPD) tends to be slower, characterized by narrow and short steps, and variation in the proportion of the phases of the gait cycle [1–5]. Regarding kinematic and kinetic parameters of gait in PD, studies indicate a lower range of motion of the hips in the coronal plane and of the pelvic obliquity, a lower flexion–extension range of the knees with a high degree of flexion in the initial contact, and the stance phase; and greater ankle dorsiflexion during the stance phase compared to healthy people [3,5]. Albani et al. [6] found that people in the early stage of PD have lower ankle power during terminal stance and a lower maximum dorsiflexion moment during the stance phase compared to healthy people. Morris et al. [4] found a significant reduction in range of motion in the sagittal plane of the hip, knee, and ankle joints, lower pelvic obliquity and rotation, and reduced hip abduction in pwPD compared to healthy older

Abbreviations: PD, Parkinson's disease; pwPD, people with Parkinson's disease; FoG, freezing of gait; pwFoG, people with freezing of gait; pwoFoG, people without freezing of gait; GRF, ground reaction forces; H&Y, Hoehn and Yahr; NFoG-Q, New Freezing of Gait Questionnaire.

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adults.

Freezing of gait (FoG) is defined as a brief episodic phenomenon of absence or marked reduction in foot progression when there is an intention to walk. Son et al. [7] observed a higher speed in the group without FoG (pwoFoG) than the group with FoG (pwFoG), and no significant difference was observed in the joint range of motion in the sagittal plane. Albani et al. [6] found no spatiotemporal differences between these groups. However, kinematic differences were observed in hip flexion at initial contact and less minimal hip flexion during the stance phase of the pwoFoG compared to the pwFoG group.

The administration of levodopa is one of the main treatments for PD. During the ON mediation, the self-selected gait speed of pwPD increases [1,8]. However, the medication induces different and inconsistent effects when looking at the spatiotemporal parameters of gait. For example, Curtze et al. [8] showed that the ON state increased speed and stride length but did not influence cadence, stride initiation, double support, and swing time. In contrast, Mondal et al. [1] showed a decrease in double stance time in the ON, a decrease in the number of steps, and an increase in step and stride lengths. In this study, the medication did not exert any difference in cadence, unilateral support time, step time, cycle time, swing time, and width of the base of support.

No studies in the literature have compared medication's effect on gait between individuals with and without FoG. In a turning task, McNeely and Earhart [9] compared the effect of medication in peolpe with and without FoG. Their results showed that in the OFF state, the pwFoG performed worse on this task. With medication, both groups improved their performance on the task, but the pwFoG showed a more pronounced improvement and reached a performance like that of the pwoFoG in the ON state. The authors concluded that this higher level of improvement occurred because the pwFoG has a greater degree of disability in the OFF state and, therefore, a greater potential for improvement. It is possible to assume that the improvement in gait induced by the medication may follow this pattern, being more evident in the pwFoG. However, the authors cite as a limitation the fact that the pwFoG took a higher drug dosage than the pwoFoG. Given this limitation, it is interesting to evaluate this hypothesis, controlling for this and other possible clinical differences between these groups.

Although these studies have evaluated kinematic and kinetic parameters of gait in PD, these articles have not analyzed the interaction between FoG and medication. The Morris study [4] evaluated pwPD in the ON and OFF conditions of the medication. However, these people were not classified with or without FoG. The articles by Albani and Son [6,7] presented the gait variations of pwPD classified as pwFoG or pwoFoG in the OFF medication. Therefore, our study aims to analyze the effect of the disease, FoG, and medication on the lower limb joint kinematics and ground reaction force parameters of gait in people with Parkinson's disease. Two specific objectives were evaluated: (1) the interaction of freezing of gait and medication in the gait of pwPD; (2) the effects of Parkinson's disease compared to healthy age-matched people. We hypothesized: (1) there is lower joint amplitude and ground reaction force during gait of pwPD compared to healthy age-matched people; (2) there are lower joint amplitudes and ground reaction force during gait in the OFF compared to ON medication in pwPD; (3) there are lower joint amplitudes and lower ground reaction force during gait in pwFoG compared to pwoFoG; and (4) there are similoar joint amplitudes and ground reaction force during gait in pwFoG in the ON compared to pwoFoG in the OFF.

2. Methods

An open data set was used for the gait of pwPD [10] and another for healthy age-matched people [11]. The two data sets were collected in the same laboratory and experimental procedure. Below we describe the methods and data available in these data sets.

2.1. Participants

Twenty-two people participated in this study, 11 with FoG (17 men and 5 women; mean age = 64.1 years, SD = 10.5) with a clinical diagnosis of idiopathic PD. A movement disorders specialist confirmed the diagnosis of idiopathic PD by UK Parkinson's Disease Society Brain Bank diagnostic criteria. These people were Hoehn and Yahr stage (H&Y) range between 1 and 4 (Med = 2; minimum = 1; maximum = 4); disease duration of 9.9 ± 6.0; they obtained a mean score of 23.05 (SD = 4.28) on the Montreal Cognitive Assessment (MoCA), with self-declaration that they had no neurological impairment other than PD or musculoskeletal changes that could interfere with the task performance.

Eighteen participants were selected from the database [11] to match them by age with the participants with PD collected (10 men and 8 women; mean age = 62.7 years; SD = 8.0). The selected participants did not present any lower extremity injuries in the last six months before data collection and did not report any orthopedic or neurological disease that could interfere with their gait patterns.

2.2. Task and equipment

Participants performed the tasks barefoot and in comfortable clothes. Participants walked on the ground on a 10-meter-long walkway at a comfortable, self-selected speed. The participant's movement while walking on a 10-meter-long walkway was measured using a motion capture system composed of 12 cameras with five force platforms. The protocol consists of 26 anatomical reference points on the individual's body, according to the model proposed by Leardini [12].

2.3. Experimental design and procedures

PD patients were divided into two groups according to the presence (FoG, n = 11) or absence (pwoFoG, n = 11) of the FoG symptom. FoG was confirmed by score 1 of item 1 of the New Freezing of Gait Questionnaire, NFoQ-Q [13]. PD patients participated in two experimental sessions: one of the sessions in the ON and the other in the OFF medication. To be considered ON status, participants had taken medications one hour before starting the session to ensure dose stabilization. In the OFF, participants spent at least 12 h without taking any medication for Parkinson's disease at the time of the experiment. The order of sessions was randomized among participants.

The initial evaluations consisted of an anamnesis form to collect clinical data, medication, and time of diagnosis of the disease. Two physical therapists applied the following rating scales: part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III), H&Y, nFoGQ, MoCA, and the Balance Assessment System Mini-Test scale (Mini-BESTest).

After the initial clinical assessments, participants were given a 10-minute rest period. Participants performed 20 trials of the experimental task in each condition. Participants were instructed to walk at a comfortable, self-selected speed for 10 m.

2.4. Data analysis

Although there were two freezing events during the experimental collections, the analysis disregarded both trials. Only the side of the body most affected by pwPD was analyzed. Asymmetry was defined as the difference between the UPDRS scores in the OFF condition plus the right and left sides of the body (items 3.3–3.9 and 3.15). The side of the body most affected was defined as the side with the highest UPDRS score. For healthy people, half of the people were evaluated on the right side and the other half on the left side.

Data from cd3 files were processed and analyzed in Visual 3D (C-motion) software. For the joint angles, the following variables were calculated: (a) peak hip flexion; (b) peak hip extension; (c) knee flexion before initial contact; (d) peak knee flexion in loading response; (e)

minimal knee flexion in terminal stance; (f) peak knee flexion during the swing phase; (g) peak ankle plantar flexion in loading response; (h) peak ankle dorsiflexion at mid-stance; (i) peak ankle plantar flexion; (j) peak ankle dorsiflexion during the swing phase; (k) mean pelvic tilt; (l) amplitude of pelvic obliquity; (m) amplitude of pelvic rotation; (n) amplitude of add/abduction of the hip; (o) amplitude of knee add/abduction. The ground reaction force (GRF) components data were temporally normalized, and their magnitude was normalized by body weight. In addition, the magnitude of the first and second peaks of the vertical component of the GRF was calculated.

2.5. Statistical analysis

The homogeneity of variances and normality in the data distribution and residuals was analyzed using the Levene and Shapiro-Wilk tests, respectively. In cases of non-normal data, the choice of data normalization method was selected from the Pearson P statistical function divided by the degrees of freedom (P/df). Clinical scales were analyzed using 2-way ANOVA (PD group × medication). For kinematics and kinetics, linear mixed-effects models were fitted, using the Restricted Maximum Likelihood Estimation (REML), to investigate whether the results differ between groups (pwFoG and pwoFoG) and medication (ON and OFF), controlling for differences between groups found in demographic characteristics and clinical scales (disease duration, L-Dopa equivalent, and the UPDRS-III score). In addition, the REML estimate was used to avoid bias due to the sample size. Participants were considered random intercepts to account for repeated measurements within each participant. To compare the effect of the disease with the control group, the analysis of variance test (ANOVA) was used for the groups (control, pwFoG, and pwoFoG) separately, under ON and OFF conditions. The level of significance for all analyzes was set at $\alpha = 0.05$, Bonferroni's post hoc was used. All *p* values from the tests described in this study were corrected by the Bonferroni method. Partial eta squared was reported, with 0.01 indicating a small effect, 0.06 indicating a medium effect and 0.14 or higher indicating a large effect. The analyzes were performed using the R program (version 4.1.1).

3. Results

3.1. Participants

The demographic, anthropometric and clinical characteristics of the participants are described in Table 1. The groups showed no significant difference in age, weight, and height. There was no significant difference in disease duration between the pwFoG and pwoFoG groups, although the pwFoG group presented higher means and a large effect size. Regarding the MoCA, Hoehn & Yahr, UPDRS-III, and Mini-BESTest clinical tests, only the latter showed a significant difference in the medication.

3.2. Gait parameters

Fig. 1 presents the boxplot of the kinematic and kinetic variables.

Table 2 presents the p-values from the statistical analysis performed using the linear mixed effects model controlled for the time of disease, L-Dopa equivalent, and UPDRS-III.

There were significant differences between the pwFoG and pwoFoG groups for knee flexion before initial contact, minimal knee flexion at terminal stance, peak ankle plantar flexion in loading response, and peak ankle dorsiflexion during the swing phase. The pwFoG group presented greater knee flexion at initial contact, greater minimal knee flexion in terminal stance, lower ankle plantar flexion peak in load response, constant dorsiflexion during load response, and greater ankle dorsiflexion during the swing phase compared to the pwoFoG group. Regarding the effect of medication, there were significant differences between ON and OFF regarding peak knee flexion during the swing phase, range of pelvic rotation, and range of hip add/abduction. In the ON, both groups presented a greater knee flexion peak during the swing phase, a greater amplitude of pelvic rotation, and a hip add/abduction range compared to the OFF.

Table 3 presents the p values resulting from the statistical analysis performed using the ANOVA test comparing the PD group in the medication ON and the control group (PD ON × control) and the PD group in

Table 1
Means (standard deviations) of the demographic, anthropometric and clinical characteristics of the participants.

Clinical	Control	PD pwFoG		PD pwoFoG		p-value (partial eta squared)		
		ON	OFF	ON	OFF	Group	Medication	Group*Medication
Demographics and Anthropometrics								
Man/Woman (n)	8/10	8/3		9/2		–		
Age (years)	62.72	62.27		65.91		0.606		
	(7.97)	(12.12)		(8.82)		(0.03)		
Weight (kg)	66.92	68.01		74.83		0.176		
	(10.06)	(10.75)		(13.24)		(0.03)		
Height (cm)	161.83	165.59		168.00		0.151		
	(9.54)	(6.41)		(7.77)		(0.03)		
Clinical								
Time of disease (years)	–	12.00	–	7.73	–	0.091	–	–
		(5.78)		(5.48)		(0.14)		
L-Dopa equivalent units (mg•day^{-1})	–	1088.18	–	551.55	–	0.018	–	–
		(566.55)		(290.82)		(0.29)		
Hoehn & Yahr (score)	–	2.45	2.54	2.09	2.18	0.237	0.181	0.784
		(0.82)	(0.68)	(0.53)	(0.60)	(0.07)	(0.09)	(0.01)
MoCA (score)	–	24.18	23.73	21.91	23.00	0.645	0.578	0.228
		(2.67)	(2.72)	(5.34)	(5.35)	(0.01)	(0.01)	(0.06)
UPDRS-III (score)	–	24.00	29.18	17.91	23.73	0.078	0.278	0.142
		(13.71)	(15.12)	(7.70)	(7.71)	(0.15)	(0.06)	(0.10)
UPDRS-III dyskinesia (score)		5.73	5.73	4.91	4.55	0.156	0.063	0.131
		(4.15)	(3.77)	(4.04)	(2.34)	(0.05)	(0.08)	(0.06)
Mini-BESTest (score)	–	25.00	23.64	25.91	24.73	0.666	0.046 *	0.881
		(6.59)	(6.99)	(3.64)	(4.07)	(0.01)	(0.18)	(0.01)

FoG = freezing of gait; pwoFoG = no freezing of gait; ON medication = assessment performed 1 h after administration of medications; OFF medication = assessment performed 12 h after administration of medications; MoCA = Montreal Cognitive Assement scale; UPDRS-III = Unified Parkinson's Disease Assessment Scale, motor part (total score and separate score for items 5 – stiffness; and 12 – gait); Mini-BESTest = Mini-Test of Balance Assessment System.

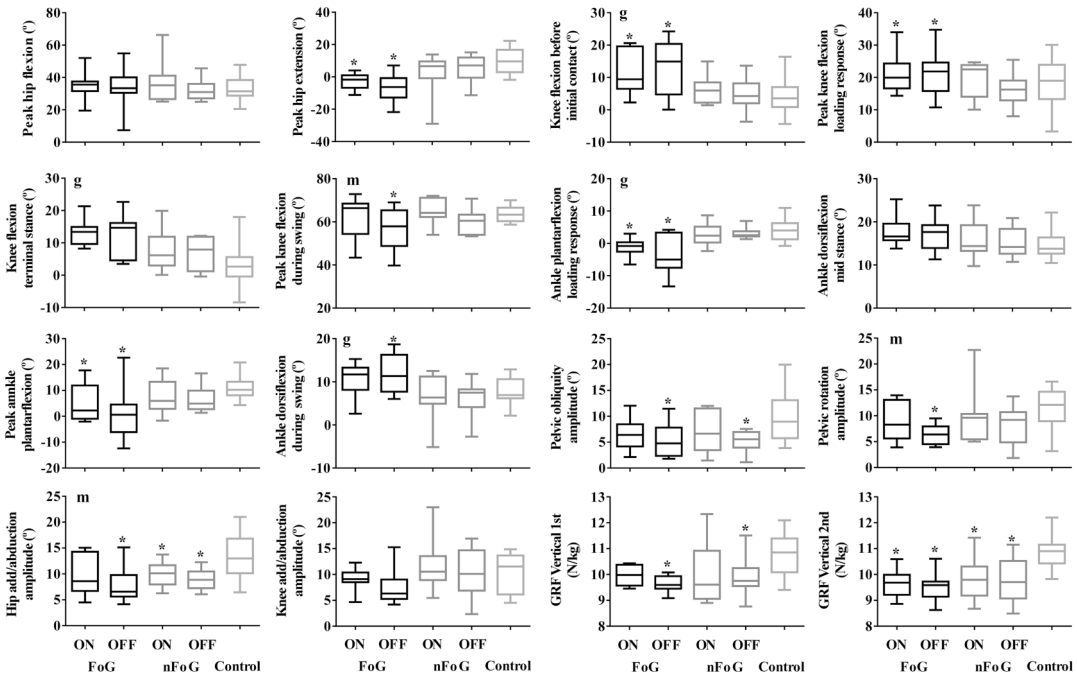

Fig. 1. Boxplot of kinematic and kinetic variables of participants with Parkinson's disease with and without freezing of gait and the control group of healthy control. * p-value < 0.05 in the ANOVA test and post-hoc Bonferroni compared to the control group; ^{g} p-value < 0.05 in the "Group" factor in the linear mixed effects model; ^{m} p-value < 0.05 in the factor "Medication status" in the linear model of mixed effects.

the medication OFF and the Control group (PD OFF × control).

pwFoG group had lower peak hip extension, greater knee flexion before initial contact and loading response, less plantar flexion in loading response, lower peak plantar flexion, and lower hip add/abduction amplitude compared to the control group. In addition, the pwFoG and pwoFoG groups had lower pelvic obliquity amplitude in the OFF compared to the control. However, during the ON, there was no significant difference in this analysis. The same occurred with the pwFoG group in the OFF for a lower peak knee flexion, greater dorsiflexion during the swing phase, and lower range of pelvic rotation compared to the control group, which during the ON did not show significant differences. Regarding the kinetic parameters, the pwFoG and pwoFoG groups had a lower first vertical GRF peak (load response) in the OFF condition compared to the control, which had no significant differences during the ON. Regarding the second peak of vertical GRF (propulsion), both pwFoG and pwoFoG groups in ON and OFF conditions had lower magnitudes than the control group.

4. Discussion

This study aims to analyze the effect of FoG and medication on the kinematic and kinetic parameters of gait in people with Parkinson's disease.

4.1. Effect of disease

Both groups with PD had a lower amplitude of pelvic obliquity and a lower first peak of vertical GRF (load response) in the OFF compared to the control, which did not occur in the ON. This may indicate an effect of the medication on these gait parameters compared to healthy people. The use of dopaminergic medication reduces the effects of co-contraction and bradykinesia present in PD, and the improvement of these symptoms provides a greater range of motion and generation of forces in the gait of these people. Regardless of medication, both groups with PD had a lower second peak of vertical GRF (propulsion) compared to the control group. This result indicates a general difficulty of pwPD regarding the generation of propulsion forces compared to healthy people. The lower application of forces in the transition from the stance phase to the swing phase provides lower spatiotemporal gait performance, demonstrated by a shorter step length, lower gait speed, and lower percentage of the swing phase [1–7]. Overall, our results reinforce the evidence for a major function of the basal ganglia in movement control, which is the preservation of a motor set predetermined by the cortical motor areas to enable the proper execution of a motor plan. Normally, the basal ganglia fit the cortically predetermined stride length to the objective of the locomotor task. The predetermined stride length is then executed by modifying all three joints of the lower limbs in three movement planes. In pwPD, the basal ganglia cannot match the preselected stride length to the intended size, resulting in a mismatch in movement amplitude across all joints.

4.2. Effect of freezing of gait

Our results showed that pwFoG had greater knee flexion at initial contact, greater minimal knee flexion at terminal stance, lower ankle plantar flexion peak in loading response, and greater ankle dorsiflexion during the swing phase than pwoFoG. The pwFoG showed differences mainly in the distal joints of the lower limbs, such as the ankle and knee, causing a more flexed posture than the pwoFoG. There are indications in the literature regarding the distal-proximal progression of deficits in the lower limbs in pwPD. Albani et al. [6] evaluated groups of pwPD separated by time of disease, and they found that the progression of deficits between groups occurred first in distal joints and later in proximal joints. Yungher et al. [14] identified high-frequency oscillation patterns of the lower limbs preceding the occurrence of freezing, which progress in a distal-proximal (from the feet to the pelvis). The magnitude of this oscillation frequency tends to decrease between segments of the lower limbs, also in a distal-proximal. These freezing events' characteristics suggest that they are driven by a high oscillation of the feet and ankles and consecutively damped from the bottom to the top. Distal limb motions are controlled by the cortico-subcortical system (basal ganglia and cortex), whereas the reticulospinal system is primarily in charge of controlling pelvic motion. These changes may also be related to a higher mean anterior pelvic tilt. Although they did not show significant

Table 2
P-values (partial eta squared) resulting from the ANOVA for the linear mixed-effect model controlled for covariates for kinematics and kinetics.

	Group	Condition	Group*Condition
Kinematics			
Peak hip flexion	0.577 (0.02)	0.206 (0.08)	0.237 (0.07)
Peak hip extension	0.197 (0.09)	0.535 (0.02)	0.045 * (0.18)
Knee flexion before initial contact	0.039 * (0.22)	0.432 (0.03)	0.245 (0.06)
Peak knee flexion in loading response	0.268 (0.07)	0.089 (0.15)	0.095 (0.14)
Minimal knee flexion in terminal stance	0.033 * (0.23)	0.239 (0.07)	0.888 (0.01)
Peak knee flexion during the swing phase	0.231 (0.09)	0.009 * (0.33)	0.570 (0.02)
Peak ankle plantar flexion in loading response	0.025 * (0.25)	0.691 (0.01)	0.784 (0.01)
Peak ankle dorsiflexion at mid stance	0.296 (0.06)	0.324 (0.05)	0.943 (0.01)
Peak ankle plantar flexion	0.181 (0.12)	0.234 (0.08)	0.209 (0.09)
Peak ankle dorsiflexion during the swing phase	0.043 * (0.21)	0.762 (0.01)	0.131 (0.11)
Mean pelvic tilt	0.947 (0.01)	0.928 (0.01)	0.159 (0.09)
Amplitude of pelvic obliquity	0.542 (0.03)	0.085 (0.17)	0.655 (0.01)
Amplitude of pelvic rotation	0.577 (0.02)	0.033 * (0.21)	0.304 (0.05)
Amplitude of add/abduction of the hip	0.136 (0.12)	0.021 * (0.24)	0.276 (0.06)
Amplitude of knee add/abduction	0.117 (0.13)	0.071 (0.15)	0.694 (0.01)
Kinetics			
GRF Vertical 1st	0.718 (0.01)	0.251 (0.01)	0.162 (0.11)
GRF Vertical 2nd	0.466 (0.04)	0.547 (0.02)	0.607 (0.02)

* indicates significant difference.

Table 3
P-values (partial eta squared) resulting from the ANOVA test comparing the group with Parkinson's disease in the ON and control (PD ON × control) and the group with Parkinson's disease in the OFF medication and control (PD OFF × control).

	PD ON × control	**PD OFF × control**
Kinematics		
Peak hip flexion	0.624 (0.03)	0.718 (0.02)
Peak hip extension	**0.001** * (0.32)	**0.001** * **(0.46)**
Knee flexion before initial contact	**0.001** * (0.29)	**0.007** * (0.24)
Peak knee flexion in loading response	0.532 (0.03)	0.236 (0.08)
Minimal knee flexion in terminal stance	**0.001** * (0.41)	**0.001** * (0.30)
Peak knee flexion during the swing phase	0.705 (0.19)	**0.046** * (0.15)
Peak ankle plantar flexion in loading response	**0.001** * (0.31)	**0.016** * (0.20)
Peak ankle dorsiflexion at mid stance	0.061 (0.14)	0.113 (0.11)
Peak ankle plantar flexion	**0.024** * **(0.18)**	**0.001** * (0.32)
Peak ankle dorsiflexion during the swing phase	**0.018** * **(0.19)**	**0.003** * (0.27)
Mean pelvic tilt	0.113 (0.11)	0.053 (0.15)
Amplitude of pelvic obliquity	0.051 (0.15)	**0.001** * (0.32)
Amplitude of pelvic rotation	0.230 (0.08)	**0.002** * (0.28)
Amplitude of add/abduction of the hip	**0.010** * **(0.22)**	**0.001** * (0.36)
Amplitude of knee add/abduction	0.189 (0.09)	0.351 (0.05)
Kinetics		
GRF Vertical 1st	**0.018** * **(0.20)**	**0.001** * (0.40)
GRF Vertical 2nd	**0.001** * (0.41)	**0.001** * (0.47)

* indicates significant difference.

differences in the analysis, they led to a more flexed posture, a characteristic of patients with PD [15]. Albani et al. [6] noted kinematic differences in hip flexion at initial contact and less minimal hip flexion during the stance phase in the pwoFoG compared to the pwFoG. Despite the differences between Albani's results and our results, it is worth mentioning that the statistical model used in Albani's article does not mention covariates, as they were used in this research. Therefore, the differences may be biased by confounding variables, such as the disease duration between the groups.

4.3. Effect of medication

Regarding the effect of the medication, both groups presented, in the ON, greater peak knee flexion during the swing phase, a greater amplitude of pelvic rotation, and a greater amplitude of hip adduction/adduction compared to the OFF. Our results suggest an action of the medication on the kinematic parameters of gait in distal and proximal joints. Studies show that levodopa does not affect axial hypertonia, and there are indications that levodopa decreases the amplitude of basal muscle activity in distal muscles but not in proximal muscles during quiet posture [16]. The lateral corticospinal tract mediates distal limb control (pyramidal tract). The proximal and axial muscles are controlled by the uncrossed portion of the pyramidal tracts (ventral corticospinal tracts) and the tectospinal, vestibulospinal, and reticulospinal tracts arising in the brainstem that bilaterally innervate the proximal and axial muscles. These various mechanisms might be why levodopa replacement therapy increases limb rigidity but not axial rigidity [17]. Despite this, dopaminergic replacement therapy reduces the co-contraction of postural synergies and the bradykinesia of voluntary movements and gait. Reducing muscle co-contraction in patients with PD improves the ability to generate forces and more effective postural responses. Thus, the reduction in co-contractions and bradykinesia in the ON of the medication may explain the improvement in the joint performance of gait in patients with PD, represented by greater ranges of motion of the knee, hip, and pelvis, leading to a greater step length and gait speed.

4.4. Limitations

The small sample means that our results must be considered with caution. We analyzed only the joint kinematics of the lower limbs and not the whole-body kinematic data. UPDRS score was applied by physical therapists rather than movement disorders-trained physicians. Additionally, NFoG-Q has limitations. Despite being validated and used worldwide, the NFoG-Q evaluates the occurrence and duration of freezing episodes only during step initiation and turning. Furthermore, the adequacy of responses may depend on the level of education and the cognitive status and memory of the patient or caregiver [13].

5. Conclusion

Our results indicated that: (1) pwPD presents a lower application of ground reaction forces during the impulse period compared to healthy people, causing lower gait performances, such as reduced step length and gait speed; (2) FoG mainly affects distal joints, such as the ankle and knee, in the gait of pwPD; (3) people in the ON showed changes in the range of motion of both distal and proximal joints, which may explain the increase in step length and gait speed expected with the use of L-Dopa; and (4) contrary to the hypothesis, the medication showed improvements in the kinematic and kinetic parameters of the gait of people with pwFoG and pwoFoG equally. A rostral to caudal degeneration of locomotor control centers may be expressed in PD by the distal to proximal progression of lower limb disability during locomotion. Our study provides subsidies for more specific rehabilitation protocols by showing which joints kinematics are most involved in PD and FoG.

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CRediT authorship contribution statement

Thiago Kenzo Fujioka Shida: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Claudia Eunice Neves de Oliveira:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Débora da Silva Fragoso de Campos:** Data curation, Investigation, Methodology, Writing – original draft. **Emanuele Los Angeles:** Investigation, Methodology, Writing – original draft. **Claudionor Bernardo:** Investigation, Methodology. **Luana dos Santos de Oliveira:** Investigation, Methodology. **Layla Cupertino Salloum e Silva:** Investigation, Methodology. **Thayna Magalhães Novaes:** Investigation, Methodology. **Solaiman Shokur:** Visualization, Writing – review & editing. **Mohamed Bouri:** Visualization, Writing – review & editing. **Daniel Boari Coelho:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neulet.2023.137250.

References

[1] B. Mondal, S. Choudhury, R. Banerjee, K. Chatterjee, S. Ghosal, S.S. Anand, H. Kumar, Analysis of gait in Parkinson's disease reflecting the effect of l-DOPA, Ann. Mov. Disord. 2 (2019) 21–27, https://doi.org/10.4103/AOMD.AOMD_19_18.
[2] J.D. O'Sullivan, C.M. Said, L.C. Dillon, M. Hoffman, A.J. Hughes, Gait analysis in patients with Parkinson's disease and motor fluctuations: influence of levodopa and comparison with other measures of motor function, Mov. Disord. 13 (1998) 900–906, https://doi.org/10.1002/mds.870130607.
[3] A.P.J. Zanardi, E.S. da Silva, R.R. Costa, E. Passos-Monteiro, I.O. Dos Santos, L.F. M. Kruel, L.A. Peyre-Tartaruga, Gait parameters of Parkinson's disease compared with healthy controls: a systematic review and meta-analysis, Sci. Rep. 11 (2021) 752, https://doi.org/10.1038/s41598-020-80768-2.
[4] M. Morris, R. Iansek, J. McGinley, T. Matyas, F. Huxham, Three-dimensional gait biomechanics in Parkinson's disease: evidence for a centrally mediated amplitude regulation disorder, Mov. Disord. 20 (2005) 40–50, https://doi.org/10.1002/mds.20278.
[5] M. Pistacchi, M. Gioulis, F. Sanson, E. De Giovannini, G. Filippi, F. Rossetto, S. Zambito Marsala, Gait analysis and clinical correlations in early Parkinson's disease, Funct. Neurol. 32 (2017) 28–34, https://doi.org/10.11138/fneur/2017.32.1.028.
[6] G. Albani, V. Cimolin, A. Fasano, C. Trotti, M. Galli, A. Mauro, "Masters and servants" in parkinsonian gait: a three-dimensional analysis of biomechanical changes sensitive to disease progression, Funct. Neurol. 29 (2014) 99–105.
[7] M. Son, S.M. Cheon, C. Youm, Y. Kim, J.W. Kim, Impacts of freezing of gait on forward and backward gait in Parkinson's disease, Gait Posture 61 (2018) 320–324, https://doi.org/10.1016/j.gaitpost.2018.01.034.
[8] C. Curtze, J.G. Nutt, P. Carlson-Kuhta, M. Mancini, F.B. Horak, Levodopa is a double-edged sword for balance and gait in people with Parkinson's disease, Mov. Disord. 30 (2015) 1361–1370, https://doi.org/10.1002/mds.26269.
[9] M.E. McNeely, G.M. Earhart, The effects of medication on turning in people with Parkinson disease with and without freezing of gait, J. Parkinsons Dis. 1 (2011) 259–270, https://doi.org/10.3233/JPD-2011-11030.
[10] T.K.F. Shida, T.M. Costa, C.E.N. de Oliveira, R.C. Treza, S.M. Hondo, E. Los Angeles, C. Bernardo, L.S. de Oliveira, M.J. Carvalho, D.B. Coelho, A public data set of walking full-body kinematics and kinetics in individuals with Parkinson's disease, Front. Neurosci. 17 (2023) 992585, https://doi.org/10.3389/fnins.2023.992585.
[11] C.A. Fukuchi, R.K. Fukuchi, M. Duarte, A public dataset of overground and treadmill walking kinematics and kinetics in healthy individuals, PeerJ 6 (2018) e4640, https://doi.org/10.7717/peerj.4640.
[12] A. Leardini, Z. Sawacha, G. Paolini, S. Ingrosso, R. Nativo, M.G. Benedetti, A new anatomically based protocol for gait analysis in children, Gait Posture 26 (2007) 560–571, https://doi.org/10.1016/j.gaitpost.2006.12.018.
[13] A. Nieuwboer, L. Rochester, T. Herman, W. Vandenberghe, G.E. Emil, T. Thomaes, N. Giladi, Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers, Gait Posture 30 (2009) 459–463, https://doi.org/10.1016/j.gaitpost.2009.07.108.
[14] D.A. Yungher, T.R. Morris, V. Dilda, J.M. Shine, S.L. Naismith, S.J. Lewis, S. T. Moore, Temporal characteristics of high-frequency lower-limb oscillation during freezing of gait in Parkinson's disease, Parkinsons Dis. 2014 (2014), 606427, https://doi.org/10.1155/2014/606427.
[15] A. Mirelman, P. Bonato, R. Camicioli, T.D. Ellis, N. Giladi, J.L. Hamilton, C.J. Hass, J.M. Hausdorff, E. Pelosin, Q.J. Almeida, Gait impairments in Parkinson's disease, Lancet Neurol. 18 (2019) 697–708, https://doi.org/10.1016/S1474-4422(19)30044-4.
[16] A. Burleigh, F. Horak, J. Nutt, J. Frank, Levodopa reduces muscle tone and lower extremity tremor in Parkinson's disease, Can. J. Neurol. Sci. 22 (1995) 280–285, https://doi.org/10.1017/s0317167100039470.
[17] W.G. Wright, V.S. Gurfinkel, J. Nutt, F.B. Horak, P.J. Cordo, Axial hypertonicity in Parkinson's disease: direct measurements of trunk and hip torque, Exp. Neurol. 208 (2007) 38–46, https://doi.org/10.1016/j.expneurol.2007.07.002.