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# Effect of antiparkinsonian medication on spatiotemporal gait parameters of individuals with Parkinson's disease: comparison between individuals with and without freezing of gait

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**HIGHLIGHTS**

- The gait of pwPD tends to be slower, characterized by narrow and short steps.
- Levodopa improves speed in gait in pwPD.
- Medication improved gait performance equivalently in the freezers and non-freezers.

**ABBREVIATIONS**

| | |
|---|---|
| FOG | Freezing of gait |
| Freezers | Individuals with FOG |
| H&Y | Hoehn and Yahr |
| H1 | Hypothesis 1 |
| H2 | Hypothesis 2 |
| LEDD | Levodopa-equivalent daily dose |
| Mini-BESTest | Balance Assessment System Mini-Test scale |
| MoCA | Montreal Cognitive Scale Assessment |
| NFOG-Q | New Freezing of Gait Questionnaire |
| Non-freezers | Individuals without FOG |
| OFF | ~12 h after the last medication ingestion |
| ON | 1 h after medication ingestion |
| PD | Parkinson's disease |
| PIGD | Postural instability and gait disturbances |
| TD | Dominant tremor |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| UPDRS_II | Activities of daily living |
| UPDRS_III | Motor symptoms |

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**BACKGROUND:** The gait of individuals with Parkinson's disease (PD) tends to be slower, characterized by narrow and short steps. During the medication, the self-selected gait speed of individuals with PD increases. However, when looking individually at the spatiotemporal parameters of gait, the medication induces different and not always consistent effects. However, the effects of medication and freezing of gait during walking in individuals with PD are unknown.
**AIM:** The present study aims to analyze the effect of antiparkinsonian medication and freezing of gait (FoG) on spatiotemporal gait parameters in individuals with PD.
**METHOD:** For this purpose, we compared gait parameters in individuals with FoG (freezers, *n* = 11) and without FoG (non-freezers, *n* = 11). Spatiotemporal gait parameters (speed, cadence, step length, step time, step width, stride length, stride time, swing phase, and double support) and clinical scales (parts II and III of the Unified Parkinson's Disease Rating Scale, Hoehn and Yahr, Montreal Cognitive Assessment questionnaire and Mini-Test scale of Balance Assessment System) were analyzed in two experimental sessions, counterbalanced between individuals: one in the ON medication state (1 h after ingestion), and another in the OFF medication state (~12 h after the last ingestion). Linear mixed effects models 2 (group: freezers X non-freezers) X 2 (condition: ON X OFF) were used.
**RESULTS:** We found that gait speed, stride, and step length were significantly higher in the ON than in the OFF condition for both freezers and non-freezers, and significantly lower in the freezers than in the non-freezers, regardless of the medication state.
**INTERPRETATION:** These results indicate that medication improved gait performance equivalently in both freezers and non-freezers.

**KEYWORDS**: Movement disorders | Levodopa | Motor control | Biomechanics

## INTRODUCTION

The gait of individuals with Parkinson's disease (PD) tends to be slower, characterized by narrow and short steps, flexed trunk, little or no arm swing [1], and slow and spasmodic turning [2]. When specifically analyzing the spatiotemporal parameters of gait in individuals with PD compared to healthy individuals, studies have shown a decrease in speed [3,4,5,6], an increase in the number of steps [5], a decrease in step length [4,5] and stride length [5]; shorter duration of swing phase and single-leg stance phase [5]; and longer duration of the double support phase [5,7]. This change in gait pattern is considered one of the symptoms that most affect the quality of life of individuals with PD, responsible for about 50% of the individual falls [8], which can result in hospitalization and involvement of motor function.

In addition to the classic characteristics of parkinsonian gait, some individuals have freezing of gait (FoG), defined as "brief and episodic absence or marked reduction in the forward progression of the feet, despite the intention to walk" [9]. Individuals with this symptom

often report that their feet are stuck to the ground, making it impossible to perform the step for a few moments. These episodes affect individuals' gait, increasing the risk of falling and decreasing independence and quality of life. FoG is usually a transient and short-lived episode. It can be triggered at different moments of gait, such as the beginning of the movement, turning, and passing obstacles, among others. As the disease progresses, FoG may increase in both frequency and duration. Individuals with FoG (freezers), when compared to individuals without FoG (non-freezers), have more severe motor and cognitive symptoms, longer duration of disease, use a higher dosage of antiparkinsonian medication [10], and have greater cortical activation during gait, indicating less automaticity [11]. Furthermore, a longitudinal study by Glover et al. [12] showed that freezers had more pronounced gait changes with disease progression evaluated from stride length and speed, duration of the swing phase, and single support compared to non-freezers. Landes et al. [13] showed that intra-patient variability in spatiotemporal gait parameters in freezers is much higher compared to other groups.

One of the main drug treatments for PD aims at dopaminergic replacement based on the administration of levodopa, an immediate precursor of dopamine, capable of overcoming the blood-brain barrier and entering the brain, unlike exogenous dopamine. Once in the brain, levodopa rapidly converts to dopamine through simple enzymatic reactions. Dopaminergic replacement therapy is made up of two main components. The first is characterized by short-term effects (about a few hours), related to the concentration of circulating dopamine. The second is characterized by long-lasting effects (about days to weeks), related to neural plasticity induced by dopaminergic signaling [14]. However, there is no evidence to demonstrate the decrease in disease progression with the conventionally used drug treatment [15]. However, fluctuations in the motor response dependent on medication administration are observed, known as the ON-OFF phenomenon, characterized by improvement of the motor pattern in the ON medication state and motor worsening with the decrease in the blood concentration of the medication [14]. Specifically, regarding gait, during the ON medication, the self-selected gait speed of individuals with PD increases [5,16]. However, when looking individually at the spatiotemporal parameters of gait, the drug induces different and not always consistent effects. For example, Curtze et al. [16] showed that the ON state increased speed and stride length but did not influence cadence, step initiation, double support time, and swing time.

On the other hand, Mondal et al. [5] showed a decrease in the double support time in the ON state, a decrease in the number of steps, and an increase in step and stride lengths. Furthermore, in the same study, the medication did not affect cadence, unilateral support time, step time, cycle time, swing time, and width of the support base. Thus, it is still unclear what the effect of dopaminergic medication would be on the spatiotemporal parameters of the gait of the person with PD, causing different explanations to appear in the literature. For example, Curtze et al. [16] argue that levodopa improves gait without changing the parameters related to its dynamic stability. On the other hand, Mondal et al. [5] consider that parameters related to gait rhythm are resistant to levodopa and that parameters that require caloric expenditure (i.e., stride length) are sensitive to medication.

Suppa et al. [17] analyze the effect of medication and FoG on spatiotemporal gait parameters. The authors found a non-significant effect of the fact FoG, whereas the factor "dopaminergic therapy" was significant only for speed, but not for stride length, stride time, and cadence. ANOVA also showed a significant interaction between factors FoG and "dopaminergic therapy" for speed, stride length, and stride time. However, the authors measure gait during a modified 3-m Timed Up and Go, resulting in a limited number of steps required for measurement [18]. In a turning task, McNeely and Earhart [19] compared the effect of medication on subjects with and without FoG. Their results showed that in the OFF state, the group with FoG performed worse on this task. However, with medication, both groups improved their performance on the task. Still, the group with FoG showed a more pronounced improvement and reached a performance similar to that of the group without FoG in the ON medication state [19]. The authors concluded that this greater improvement occurred because the group with FoG has a greater degree of disability in the OFF state and, therefore, a greater potential for improvement. Therefore, it is possible to assume that the improvement in gait induced by the medication may follow this pattern, being more evident in the group with FoG. However, the authors cite as a limitation the fact that the group with FoG took a higher drug dosage than the group without FoG. Given this limitation, it is interesting to evaluate this hypothesis, controlling for it and other possible clinical differences between these groups.

This study aims to analyze the effect of antiparkinsonian medication on gait spatiotemporal parameters, comparing freezers versus non-freezers, in individuals with PD. The following hypotheses were formulated: (H1) The medication improves the gait both in freezers and non-freezers; (H2) the medication induces a more pronounced improvement in gait in freezers.

## METHODS

### Participants

The study included 22 individuals (5 women; mean age = 64.1 years; disease duration = 10.5 years) with a clinical diagnosis of idiopathic PD made by a neurologist. Eleven participants were freezers (based on the New Freezing questionnaire of Gait questionnaire, NFOG-Q) and 11 were non-freezers. Participants were between stages 1 and 4 of PD, and classified by the criteria of the modified Hoehn and Yahr (H&Y) scale (Median = 2; minimum = 1; maximum = 4), obtained a minimum score of 15 (Median = 24; minimum = 15; maximum = 30) on the Montreal Cognitive Scale Assessment (MoCA), with self-declaration of no neurological impairment other than PD

or musculoskeletal alterations that could impair task performance. Participants were informed about the objectives, benefits, and risks associated with the study. All signed the informed consent form by the procedures approved by the local research ethics committee (CAAE number 21948619.6.0000.5594).

### Task and equipment

Participants walked barefoot at a self-selected comfortable speed over a 10-m long walkway for gait assessment. At ground level, there was a pressure system (FDM, Zebris, sampling rate: 100Hz, accuracy 5%), composed of two coupled electronic walkways in the middle of the walkway. The Zebris system is an electronic walkway with pressure-activated sensors embedded into a 60-cm wide x 6-m long mat. With this equipment, it is possible to measure gait parameters in real time by detecting the change in pressure exerted by the participant's feet when walking on the footbridge. Data were automatically transferred to a computer connected to the system to be further processed and analyzed off-line.

### Procedures

The volunteers participated in two experimental sessions at the Laboratory of Biomechanics and Motor Control at the Federal University of ABC, one of the sessions being in the ON medication state and the other in the OFF state. To be considered in the ON state, participants had to have taken their dopaminergic medication one hour before starting the session to ensure dosage stabilization. In the OFF state, participants had to have been at least 12 hours without using any PD medication at the experiment's time. The order of the sessions was counterbalanced among the participants, and they were held at an interval of one week. The total dose of these drugs was converted into a levodopa-equivalent daily dose (LEDD), based on the formula developed by Tomlinson, Stowe [20].

Initial assessments consisted of an anamnesis to collect clinical data, medication dosage, and time of diagnosis of the disease. The following evaluation scales were also applied: parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS, parts II-III) to assess activities of daily living and motor symptoms, respectively, H&Y to assess disease severity, NFOG-Q to assess freezing of gait [21], MoCA questionnaire for cognitive assessment [22], the Balance Assessment System Mini-Test scale (Mini-BESTest) for assessing global body balance [23]. Classification of PD subtype into dominant tremor (TD) and postural instability and gait disturbances (PIGD) was performed according to Stebbins, Goetz [24], using the average of 8 scale items to calculate the TD score and five items for the PIGD score. Individuals whose ratio between the average of the TD/PIGD scores ≥ 1.5 were classified as subtype TD, ≤ 1 classified as subtype PIGD, and results between > 1 and < 1.5 were classified as undetermined. In addition, specific motor symptoms related to the TD (UPDRS_TD) and PIGD (UPDRS_PIGD) subtypes were assessed using the average scores of the same items used for classification. The same evaluator performed all clinical evaluations.

After the initial clinical evaluations and a 10-min rest period, the participants performed ten trials of the experimental task in each condition (ON and OFF). Participants were instructed to walk at a comfortable speed for 10 m, passing over the electronic walkway. The trials were made sequentially, with a short rest between them (<10 s). An evaluator was close by to ensure protection and prevent the participants from falling during the entire experimental procedure.

### Variables

The average result of all occurrences of a given variable in each trial was used and, subsequently, the average of the ten trials per condition for each participant. The analyzed spatiotemporal gait parameters were the following:

a. Gait speed: average speed, computed as a function of the time spent to cover the 6-m distance to cross the walkway;

b. Cadence: given by the number of steps per minute;

c. Average step length: given by the distance between the heel of one foot and the heel of the other foot in each step during gait. For analysis, an average was made between the length of the right and left steps;

d. Step time: given by the time interval obtained from two successive contacts of the feet with the ground;

e. Step width: transverse distance from the center of the heel of one foot to the center of the heel of the other;

f. Stride length: distance between two successive contacts of the same foot, measured from the heel;

g. Stride time: given by the time interval between two successive contacts of the same foot with the ground;

h. Relative time of the swing phase: given by the percentage of the stride time used in the swing phase, in which one of the feet is not in contact with the ground, being projected forward to make the next contact;

i. Total double support: given by the percentage of stride time in the double support phase, in which both feet are in contact with the ground simultaneously. This is the sum of two partial double supports.

### Data analysis

The Levene and Shapiro-Wilk tests were used to analyze the homogeneity of variances and normality in data distribution and residuals. In addition, demographic data and clinical scales were analyzed using the Wilcoxon test for intragroup comparisons (medication effect) and the Mann-Whitney U test for intergroup comparisons (FoG effect). To choose the data transformation method, the Pearson P statistical function was divided by the degrees of freedom (P/df); this ratio can be compared between the different forms of normalization and indicates which data follow the closest distribution normality (ratio close to 1). The arc-sine transformation was then used to normalize the H&Y data, and the ordered quantile transformation to normalize the spatiotemporal gait parameters and data on disease duration and medication dosage.

With the data normalized, linear mixed-effects models 2 (group: freezers X non-freezers) x 2 (medication: ON X OFF) were fitted using restricted maximum likelihood estimation to investigate whether the results of the spatiotemporal gait parameters differed between groups (freezers and non-freezers) and conditions (ON and OFF). Participants were considered random intercepts. The significance level for all analyses was set at $p < 0.05$, and Bonferroni's post hoc test was used to analyze interactions. Analyzes were performed using Minitab (Minitab 19.2, 64-bit) and R (version 4.1.1). The means and standard deviations of the untransformed values will be displayed.

## RESULTS

Of the 11 individuals in the freezer group, eight were classified with the PIGD subtype, two with the TD subtype, and one undetermined in the ON state; in the OFF state, there were 9, one, and one, respectively, for each subgroup. Of the 11 participants in the non-freezers group, four were classified with the PIGD subtype, five with the TD subtype, and two undetermined in the ON state; in the OFF state, there were two, six, and three, respectively, in each subgroup.

Table 1 presents the demographic and clinical characteristics of the participants, separated by groups. There were no significant differences between groups in terms of age, weight, height, and disease duration, although the latter showed a tendency towards statistical difference ($p = 0.06$). In addition, there were no significant differences between groups in MoCA, H&Y, UPDRS_TD, and mini-BESTest scores in the ON medication condition. However, the freezers had greater motor severity symptoms (UPDRS- III) and a higher mean score of the sub-items related to postural instability and gait disorders (UPDRS_PIGD) than the non-freezers in the ON condition. In the OFF condition, there were no significant differences between groups in MoCA, H&Y, UPDRS -III_Total, UPDRS_TD, and mini-BESTest scores. However, the freezers had a higher mean score for the sub-items related to postural instability and gait disorders (UPDRS_PIGD) than the non-freezers in the OFF condition.

### Effect of medication on clinical features

Table 2 shows the medication effect on each group's clinical characteristics. For the freezers, there was no significant differences between conditions in MoCA, H&Y, UPDRS - III_Total, UPDRS_TD, and Mini-BESTest scores. In the OFF state, the average score of the sub-items related to postural instability and gait disturbances (UPDRS_PIGD) was higher than in the ON condition in the freezers. The non-freezers did not show significant differences between conditions in MoCA, H&Y, UPDRS_PIGD, and mini-BESTest scores. In the OFF condition, the non-freezers presented greater severity of symptoms (UPDRS-III_Total) and a higher mean score of the sub-items related to dominant tremor (UPDRS_TD) when compared to the ON condition of the medication.

**Table 1.** Means and standard deviations of demographic and clinical characteristics of participants separately by the group.

| Characteristics | PD freezers | PD non-freezers | *p-value* |
|---|---|---|---|
| **Demographics and anthropometrics** | | | |
| Man/Woman (n) | 8/3 | 9/2 | |
| Age (years) | 61.5±10.98 | 64.42±8.65 | 0.15 |
| Weight (kg) | 72.06±13.52 | 70.84±12.70 | 0.73 |
| Height (cm) | 166.25±7.39 | 166.17±7.03 | 0.94 |
| **Clinics** | | | |
| NFOG – Q (score) | 18.83±5.25 | 0±0 | **<0.01** |
| Disease duration (years) | 12.5±5.66 | 8.08±5.07 | 0.07 |
| Levodopa-equivalent daily dose (mg/day) | 1085.13±527.48 | 610.55±385.69 | **0.01** |
| **ON condition clinics** | | | |
| MoCA (score) | 23.55±2.91 | 22.18±5.53 | 0.72 |
| H&Y (I / II / III / IV) | 1/5/4/1 | 1/8/2/0 | 0.25 |
| UPDRS- II (score) | 6.36±3.53 | 2.90±3.27 | **0.03** |
| UPDRS- III (score) | 29.91±14.95 | 17.64±7.86 | **0.04** |
| UPDRS_ PIGD (score) | 1.00±0.56 | 0.36±0.38 | **0.01** |
| UPDRS_TD (score) | 0.74±0.63 | 0.43±0.30 | 0.28 |
| Mini-BESTest (score) | 24.45±6.31 | 26.36±3.96 | 0.57 |
| **OFF condition clinics** | | | |
| MoCA (score) | 24.09±3.02 | 22.64±5.10 | 0.60 |
| H&Y (I / II / III / IV) | 0 / 5 / 5 / 1 | 1/8/2/0 | 0.06 |
| UPDRS- II (score) | 9.54±2.73 | 3.82±2.32 | **0.01** |
| UPDRS- III (score) | 30.09±14.81 | 22.82±7.48 | 0.19 |
| UPDRS_ PIGD (score) | 1.45±0.61 | 0.40±0.24 | **<0.01** |
| UPDRS_TD (score) | 0.93±0.86 | 0.85±0.50 | 0.74 |
| Mini-BESTest (score) | 23.00±687 | 25.36±3.98 | 0.51 |

NFOG - Q = *New Freezing of Gait Questionnaire*; MoCA = *Montreal Cognitive Assessment* scale; UPDRS-III = Unified Parkinson's Disease Rating Scale, motor part (total score and separate score for PIGD and TD subtypes); Mini-BESTest = Balance Assessment System Mini-Test.

**Table 2.** Mean and standard deviation of the clinical characteristics of the participants separated by comparisons (ON vs. OFF for the same group).

| **Freezers** | **ON** | **OFF** | **p-value** |
|---|---|---|---|
| MoCA (score) | 23.55±2.91 | 24.09±3.02 | 0.65 |
| H&Y (I / II / III / IV) | 1/5/4/1 | 0/5/5/1 | 0.17 |
| UPDRS- III (score) | 29.91±14.95 | 30.09±14.81 | 0.89 |
| UPDRS-III_ PIGD (score) | 1.00±0.56 | 1.45±0.61 | **0.01** |
| UPDRS-III_TD (score) | 0.74±0.63 | 0.93±0.86 | 0.22 |
| Mini-BESTest (score) | 24.45±6.31 | 23.00±6.87 | 0.17 |
| **Non-freezers** | **ON** | **OFF** | **p-value** |
| MoCA (score) | 22.18±5.53 | 22.64±5.10 | 0.59 |
| H&Y (I / II / III / IV) | 1/8/2/0 | 1/8/2/0 | |
| UPDRS- III (score) | 17.64±7.86 | 22.82±7.48 | **0.02** |
| UPDRS-III_ PIGD (score) | 0.36±0.38 | 0.40±0.24 | 0.80 |
| UPDRS-III_TD (score) | 0.43±0.30 | 0.85±0.50 | **0.02** |
| Mini-BESTest (score) | 26.36±3.96 | 25.36±3.98 | 0.26 |

MoCA = Montreal Cognitive Assessment scale; UPDRS-III = Unified Parkinson's Disease Rating Scale, motor part (total score and separate score for PIGD and TD subtypes); Mini-BESTest = Balance Assessment System Mini-Test.

### Gait spatiotemporal parameters

During the experimental task, no freezing of gait episodes occurred; therefore, all trials were used for gait analysis. Table 4 shows results for the gait analysis. Analysis showed group and medication main effects for speed, and the spatial parameters step length and stride length. The freezers showed significantly lower values for speed, stride length, and step length when compared to the non-freezers. Analysis of the medication effect showed that in the ON state, speed, stride length, and step were greater than in the OFF state. Regarding the gait phases, our results showed the main effect of medication for the swing phase being greater in the ON condition when compared to the OFF condition.

**Table 3.** Mean and standard deviation of spatiotemporal gait variables separated by group (freezers and non-freezers) and medication condition (ON and OFF)

| Variables | Freezers ON | Freezers OFF | Non-freezers ON | Non-freezers OFF |
|---|---|---|---|---|
| Stride length (cm) | 97.31±27.15 | 76.03±35.06 | 116.85±16.59 | 108.76±12.58 |
| Step length (cm) | 48.63±13.59 | 38.01±17.53 | 58.95±7.71 | 54.37±6.28 |
| Step width (cm) | 11.01±5.85 | 11.52±4.48 | 10.60±2.23 | 10.67±2.10 |
| Stride time (s) | 1.15±0.18 | 1.24±0.48 | 1.07±0.09 | 1.11±0.10 |
| Step time (s) | 0.57±0.09 | 0.62±0.24 | 0.54±0.04 | 0.55±0.05 |
| Cadence (stride/min) | 53.30±7.22 | 52.39±11.65 | 56.32±4.75 | 54.66±4.76 |
| Speed (m/s) | 3.17±1.10 | 2.44±1.23 | 3.96±0.80 | 3.56±0.50 |
| Swing time (%) | 33.07±5.20 | 29.49±8.81 | 36.16±1.69 | 35.40±2.43 |
| Total double support (%) | 33.83±10.43 | 42.02±20.12 | 28.30±2.85 | 29.21±4.86 |

**Table 4.** Results of the statistical model applied for analysis of gait parameters.

| | p-value | | |
|---|---|---|---|
| Variables | Group effect | Medication effect | Group*Medication |
| Stride length | **0.02** | **<0.01** | 0.25 |
| Step length | **0.01** | **<0.01** | 0.40 |
| Step width | 0.80 | 0.18 | 0.23 |
| Step time | 0.70 | 1.00 | 0.68 |
| Cadence | 0.62 | 0.73 | 0.32 |
| Speed | **0.04** | **<0.01** | 0.13 |
| Swing phase | 0.05 | **0.02** | 0.48 |
| Total double support | 0.08 | 0.17 | 0.16 |

Table 5 shows the size of clinical and spatiotemporal gait variables separated by group, medication and group-medication interaction.

**Table 5**. Effect size and confidence interval (95% CI) of the parameters separated by group, medication and interaction between group and medication. In bold are statistically significant effect sizes.

| | Group effect | | Medication Effect | | Group*Medication | |
|---|---|---|---|---|---|---|
| | Freezers On vs Non-freezers On | Freezers Off vs Non-freezers Off | Freezers On vs Freezers Off | Non-freezers On vs Non-freezers Off | Freezers On vs Non-freezers Off | Freezers Off vs Non-freezers On |
| | Effect size (95% CI) | | Effect size (95% CI) | | Effect size (95% CI) | |
| Stride length | **0.72**** (0.08, 1.36) | **0.93***** (0.22, 1.65) | **-0.78**** (-1.02, -0.54) | **-0.49*** (-0.83, -0.15) | 0.42 # (-0.29, 1.13) | **1.16***** (0.55, 1.78) |
| Step Length | **0.76**** (0.12, 1.40) | **0.93***** (0.22, 1.65) | **-0.78**** (-1.02, -0.54) | **-0.59**** (-0.99, -0.20) | 0.42 # (-0.29, 1.14) | **0.93***** (0.22, 1.65) |
| Step width | -0.07 (-0.77, 0.63) | -0.19 (-0.82,0.44) | 0.09 (-0.07, 0.24) | 0.03 (-0.23, 0.29) | -0.06 (-0.74, 0.62) | -0.21 (-0.88, 0.47) |
| Stride time | -0.41 (-1.05, 0.22) | -0.28 (-0.87,0.30) | **0.51**** (0.11, 0.91) | **0.38*** (0.13, 0.63) | -0.23 (-0.86, 0.40) | -0.35 (-0.86, 0.16) |
| Step time | -0.34 (-1.02, 0.33) | -0.28 (-0.87,0.30) | **-0.50**** (0.11, 0.90) | 0.25 (-0.09, 0.58) | -0.23 (-0.86, 0.40) | -0.33 (-0.87, 0.21) |
| Cadence | 0.42 (-0.22, 1.05) | 0.19 (-0.38,0.77) | -0.13 (-0.48, 0.23) | **-0.35*** (-0.59, -0.11) | 0.19 (-0.44, 0.81) | 0.34 (-0.20, 0.88) |
| Speed | **0.71**** (0.08, 1.35) | **0.91***** (0.24, 1.59) | **-0.67**** (-0.88, -0.46) | **-0.49*** (-0.82, -0.16) | 0.35 # (-0.36, 1.06) | **1.24***** (0.62, 1.85) |
| Speed variability | -0.16 (-0.63, 0.32) | -0.70 (-1.44,0.05) | **0.54**** (0.09, 0.99) | -0.12 (-0.49, 0.26) | -0.26 (-0.89, 0.37) | -0.61 (-1.33, 0.11) |
| Swing Phase | 0.59 (-0.02, 1.21) | 0.67 (-0.03, 1.37) | **-0.69**** (-0.85, -0.53) | **-0.45*** (-0.73, -0.17) | 0.45 (-1.14, 0.24) | **0.76**** (0.15, 1.37) |
| Total Double Support | -0.53 (-1.16, 0.10) | -0.64 (-1.33,0.06) | **0.78**** (0.65, 0.92) | **0.32*** (0.03, 0.62) | -0.44 (-1.13, 0.25) | -0.68 (-1.32, 0.04) |
| UPDRS III | **-0.82***** (-1.53, -0.11) | -0.34 (-0.93,0.25) | -0.07 (-0.39, 0.26) | **0.77**** (0.31, 1.22) | -0.41# (-1.05, 0.23) | **-0.74**** (-1.48, -0.01) |
| H&Y | -0.33 (-1.03, 0.37) | -0.53 (-1.21,0.15) | 0.11 (-0.04, 0.26) | 0 (0.0, 0.0) | -0.33 (-1.03, 0.37) | 0.53 (-1.21, 0.15) |
| MiniBest | 0.14 (-0.53, 0.81) | 0.22 (-0.41,0.84) | -0.18 (-0.39, 0.04) | -0.14 (-0.42, 0.13) | 0.05 (-0.55, 0.66) | 0.29 (-0.40, 0.98) |
| MoCA | **-0.62**** (-1.10, -0.14) | -0.13 (-0.73,0.46) | -0.03 (-0.52, 0.46) | 0.26 (-0.05, 0.58) | -0.15 (-0.53, 0.24) | **-0.67**** (-1.20, -0.14) |

* represents small effect size (<0.50), ** represents moderate effect size (< 0.80) and *** represents large effect size (≥0.80).

## DISCUSSION

The present study aimed to compare the effect of antiparkinsonian medication on the spatiotemporal gait parameters between freezers and non-freezers. It was observed that the freezers used a higher dose of medication, tended to be in a more advanced stage of the disease, and had the disease for a longer time than the non-freezers. In addition, the freezers showed greater severity of motor symptoms in the ON state and higher scores on items that indicate the PIGD subtype of the disease, both in the ON and OFF states, showing greater severity of motor symptoms related to gait and postural instability. The freezers showed lower gait speed, step length, and stride length when compared to the non-freezers, indicating greater gait impairment in individuals with FoG regardless of medication status. Corroborating the hypothesis that the medication improves gait in both the freezers and non-freezers (H1), our results showed increased gait speed, stride length, and step length in both groups. However, contrary to H2, the results indicated that the improvement in gait parameters was similar between the two groups.

During the experimental task, the freezers showed no FoG episodes across all trials. However, even without FoG, gait speed, stride, and step length were lower in the freezers when compared to the non-freezers, regardless of the assessed drug condition, indicating greater gait impairment in the freezers. Glover, Pillai [12] showed that freezers have greater gait decline with disease progression as measured by the most marked reduction in stride length, duration of the swing phase and single support, and the greatest increase in stride time variability than non-freezers. Furthermore, they found that this greater decline of gait parameters in freezers was unrelated to initial medication dosage, duration of drug therapy, or drug dose changes during the study.

Unlike our results, Vitorio, Stuart [11] found no difference in gait speed and stride length between freezers and non-freezers, in evaluation only in the OFF medication. We suggest that while the individuals in the study by Vitorio, Stuart [11] seem to have maintained this compensatory mechanism, our participants may have been unable to make such a compensation, resulting in the change found in the gait of the freezers even when controlling for clinical differences. Furthermore, our results showed that while the freezers are mostly classified with the PIGD subtype of PD, showing greater postural instability and gait disorders, the non-freezers had both subtypes in similar proportions. Although there was an improvement in the mean score of the items related to the PIGD subtype of the freezers, this improvement was not enough for this score to approach the score of the non-freezers, with maintenance of the clinical difference, reflecting the difference found in the objective gait parameters.

Regarding the effect of the medication, our results corroborate the findings of previous studies showing that the medication induces an increase in gait speed, stride and step length without altering the temporal parameters cadence, step duration, and stride duration [5,16]. Furthermore, these changes were consistent between the groups of freezers and non-freezers, indicating that the medication induced a similar improvement in gait in individuals with PD regardless of having FoG. It is known that gait speed is associated with changes in spatiotemporal parameters of gait, which vary according to the self-selected speed [25]. By analyzing gait parameters in individuals with PD, Frenkel-Toledo, Giladi [26] showed that a reduction in gait speed was associated with a decrease in the length of the stride, the duration of the swing phase, and an increase in the duration of the stride. Furthermore, Turcato, Godi [27] showed that, while walking in a straight line, spatiotemporal parameters such as cadence or stride length were not different between individuals with PD and healthy individuals when compared at the same self-selected speed. Finally, Avila de Oliveira, Bazan [28] showed through a Bayesian mediation analysis that changes in gait speed have greater explanatory power of changes in spatiotemporal parameters, thus mediating the effect of dopaminergic medication on these parameters in individuals with PD. Therefore, these results indicate that changes in spatiotemporal gait parameters are strongly related to changes in gait speed induced by the ON condition of the medication.

Self-selected gait speed is considered mechanically more efficient, as it induces less variability in stride length, optimization of muscle activation, and range of hip joint rotation, thus allowing less energy expenditure [26,29,30]. Furthermore, dopaminergic replacement from levodopa ingestion induces a reduction in bradykinesia and joint stiffness, improvement in automaticity, increased movement vigor and task engagement [14,31,32], which together can explain the increase in self-selected gait speed in the ON condition. Based on this, it is possible that antiparkinsonian medication induces improvement of gait in individuals with PD through the increase in self-selected speed, which, in turn, is associated with changes in some of the spatiotemporal gait parameters that are adjusted to this new speed. Therefore, there are not necessarily spatiotemporal parameters responsive or resistant to levodopa. Instead, they vary according to the variation in gait speed induced by dopaminergic replacement.

Finally, contrary to our expectations, the medication failed to exert a more marked improvement in gait in freezers (H2), even with the gait of this group being more debilitated than that of non-freezers in the OFF state. Therefore, unlike the more pronounced improvement of freezers found in the turning test [19], the effect of medication on gait seem to not be proportional to the degree of impairment assessed in the OFF state. McNeely and Earhart [19] proposed the hypothesis that the more pronounced improvement in freezers could be related to the higher medication dosage of these individuals; therefore, the effect could be proportional to the dosage.

It was observed in our results that the medication did not induce global improvement in motor symptoms assessed by the UPDRS-III score in the freezers. At the same time, only the non-freezers showed this improvement in the ON state score. This result leads to the assumption that some freezers have reduced responsiveness to levodopa being resistant to the medication. Alternatively, they could have an inadequate medication dosage, which could be considered a limitation of the conclusions raised about the effect of the medication between the groups. Nevertheless, when analyzing the specific score of symptoms related to the PIGD subtype, the medication significantly improved the freezers' gait, with almost all individuals showing good responsiveness to the medication to the UPDRS_PIGD score. This indicates that this supposed resistance does not apply to specific results regarding gait characteristics; therefore, this limitation probably does not interfere with our results on the effect of medication on spatiotemporal parameters of gait.

The main limitation to be considered in this study is the low responsiveness to medication observed from the UPDRS-III scores of the freezers. This indicates that the drug dosage used by some individuals in the group did not induce a relevant improvement in motor symptoms in the ON state, which could interfere with the findings related to spatiotemporal gait parameters. As a result, the improvement caused by the medication in the ON of the freezers may be underestimated. Thus, caution is needed when generalizing these results to individuals with greater responsiveness to the medication. As multiple comparisons corrections were not performed, our results need to be taken with care and can be considered as an exploratory analysis. Another limitation is that we do not know the habits regarding physical exercise and other behaviors that interact with the disease.

## CONCLUSION

The results of the present study indicated that the intake of antiparkinsonian medication by individuals with PD led to an increase in self-selected gait speed, step length, and stride length. Contrary to our expectations, this improvement occurred equally between freezers and non-freezers, so that in the medicated state the difference between groups was not attenuated regarding that observed in the non-medicated state.

## REFERENCES

1. Zampier VC, Vitorio R, Beretta VS, Jaimes DaR, Orcioli-Silva D, Santos PCR, et al. Gait bradykinesia and hypometria decrease as arm swing frequency and amplitude increase. *Neuroscience letters*. 2018;687:248-252. doi: 10.1016/j.neulet.2018.09.051.
2. Mancini M, Nutt JG, Horak FB. *Balance dysfunction in Parkinson's disease: basic mechanisms to clinical management*. Academic Press: Cambridge, MA, USA; 2019.
3. Morris ME, Mcginley J, Huxham F, Collier J, Iansek R. Constraints on the kinetic, kinematic and spatiotemporal parameters of gait in Parkinson's disease. *Human movement science.* 1999;18:461-483. doi: 10.1016/s0167-9457(99)00020-2.
4. Cheng KY, Lin WC, Chang WN, Lin TK, Tsai NW, Huang CC, et al. Factors associated with fall-related fractures in Parkinson's disease. *Parkinsonism & related disorders.* 2014;20:88-92. doi: 10.1016/j.parkreldis.2013.09.024.
5. Mondal B, Choudhury S, Banerjee R, Chatterjee K, Ghosal S, Anand SS, et al. Analysis of gait in Parkinson's disease reflecting the effect of l-DOPA. *Annals of Movement Disorders.* 2019;2:21-27. doi: 10.4103/AOMD.AOMD_19_18.
6. Orcioli-Silva D, Barbieri FA, Simieli L, Vitorio R, Santos P, Beretta VS, et al. Walking behavior over multiple obstacles in people with Parkinson's disease. *Gait & posture.* 2017;58:510-515. doi: 10.1016/j.gaitpost.2017.09.021.
7. Sofuwa O, Nieuwboer A, Desloovere K, Willems AM, Chavret F, Jonkers I. Quantitative gait analysis in Parkinson's disease: comparison with a healthy control group. *Archives of physical medicine and rehabilitation.* 2005;86:1007-1013. doi: 10.1016/j.apmr.2004.08.012.
8. Lord S, Galna B, Yarnall AJ, Morris R, Coleman S, Burn D, et al. Natural history of falls in an incident cohort of Parkinson's disease: early evolution, risk and protective features. *Journal of neurology.* 2017;264:2268-2276. doi: 10.1007/s00415-017-8620-y.
9. Giladi N, Nieuwboer A. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. *Movement Disorders.* 2008;23 Suppl 2:S423-425. doi: 10.1002/mds.21927.
10. Lord SR, Bindels H, Ketheeswaran M, Brodie MA, Lawrence AD, Close JCT, et al. Freezing of Gait in People with Parkinson's Disease: Nature, Occurrence, and Risk Factors. *J Parkinsons Dis.* 2020;10:631-640. doi: 10.3233/JPD-191813.
11. Vitorio R, Stuart S, Mancini M. Executive Control of Walking in People With Parkinson's Disease With Freezing of Gait. *Neurorehabilitation and neural repair.* 2020;34:1138-1149. doi: 10.1177/1545968320969940.
12. Glover A, Pillai L, Doerhoff S, Virmani T. Differential Gait Decline in Parkinson's Disease Enhances Discrimination of Gait Freezers from Non-Freezers. *J Parkinsons Dis.* 2020;10:1657-1673. doi: 10.3233/JPD-201961.
13. Landes RD, Glover A, Pillai L, Doerhoff S, Virmani T. Levodopa ONOFF-state freezing of gait: Defining the gait and non-motor phenotype. *PloS one.* 2022;17:e0269227. doi: 10.1371/journal.pone.0269227.
14. Albin RL, Leventhal DK. The missing, the short, and the long: Levodopa responses and dopamine actions. *Annals of neurology.* 2017;82:4-19. doi: 10.1002/ana.24961.
15. Tarazi FI, Sahli ZT, Wolny M, Mousa SA. Emerging therapies for Parkinson's disease: from bench to bedside. *Pharmacol Ther.* 2014;144:123-133. doi: 10.1016/j.pharmthera.2014.05.010.
16. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease. *Movement Disorders.* 2015;30:1361-1370. doi: 10.1002/mds.26269.
17. Suppa A, Kita A, Leodori G, Zampogna A, Nicolini E, Lorenzi P, et al. l-DOPA and Freezing of Gait in Parkinson's Disease: Objective Assessment through a Wearable Wireless System. *Frontiers in neurology.* 2017;8:406. doi: 10.3389/fneur.2017.00406.
18. Van Ancum JM, Van Schooten KS, Jonkman NH, Huijben B, Van Lummel RC, Meskers CGM, et al. Gait speed assessed by a 4-m walk test is not representative of daily-life gait speed in community-dwelling adults. *Maturitas.* 2019;121:28-34. doi: 10.1016/j.maturitas.2018.12.008.
19. Mcneely ME, Earhart GM. The effects of medication on turning in people with Parkinson disease with and without freezing of gait. *J Parkinsons Dis.* 2011;1:259-270. doi: 10.3233/JPD-2011-11030.
20. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders.* 2010;25:2649-2653. doi: 10.1002/mds.23429.
21. Nieuwboer A, Rochester L, Herman T, Vandenberghe W, Emil GE, Thomaes T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait & posture.* 2009;30:459-463. doi: 10.1016/j.gaitpost.2009.07.108.
22. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society.* 2005;53:695-699. doi: 10.1111/j.1532-5415.2005.53221.x.

23. Horak FB, Wrisley DM, Frank J. The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. *Physical therapy.* 2009;89:484-498. doi: ptj.20080071.
24. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Movement Disorders.* 2013;28:668-670. doi: 10.1002/mds.25383.
25. Fukuchi CA, Fukuchi RK, Duarte M. Effects of walking speed on gait biomechanics in healthy participants: a systematic review and meta-analysis. *Systematic reviews.* 2019;8:153. doi: 10.1186/s13643-019-1063-z.
26. Frenkel-Toledo S, Giladi N, Peretz C, Herman T, Gruendlinger L, Hausdorff JM. Effect of gait speed on gait rhythmicity in Parkinson's disease: variability of stride time and swing time respond differently. *Journal of neuroengineering and rehabilitation.* 2005;2:23. doi: 10.1186/1743-0003-2-23.
27. Turcato AM, Godi M, Giardini M, Arcolin I, Nardone A, Giordano A, et al. Abnormal gait pattern emerges during curved trajectories in high-functioning Parkinsonian patients walking in line at normal speed. *PloS one.* 2018;13:e0197264. doi: 10.1371/journal.pone.0197264.
28. Avila De Oliveira J, Bazan PR, De Oliveira CEN, Treza RC, Hondo SM, Los Angeles E, et al. The effects of levodopa in the spatiotemporal gait parameters are mediated by self-selected gait speed in Parkinson's disease. *The European journal of neuroscience.* 2021;54:8020-8028. doi: 10.1111/ejn.15522.
29. Yamasaki M, Sasaki T, Torii M. Sex difference in the pattern of lower limb movement during treadmill walking. *European journal of applied physiology and occupational physiology.* 1991;62:99-103. doi: 10.1007/BF00626763.
30. Zanardi APJ, Da Silva ES, Costa RR, Passos-Monteiro E, Dos Santos IO, Kruel LFM, et al. Gait parameters of Parkinson's disease compared with healthy controls: a systematic review and meta-analysis. *Scientific reports.* 2021;11:752. doi: 10.1038/s41598-020-80768-2.
31. Gilat M, Bell PT, Ehgoetz Martens KA, Georgiades MJ, Hall JM, Walton CC, et al. Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease. *NeuroImage.* 2017;152:207-220. doi: 10.1016/j.neuroimage.2017.02.073.
32. Stuart S, Belluscio V, Quinn JF, Mancini M. Pre-frontal Cortical Activity During Walking and Turning Is Reliable and Differentiates Across Young, Older Adults and People With Parkinson's Disease. *Frontiers in neurology.* 2019;10:536. doi: 10.3389/fneur.2019.00536.

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