Objective and self-perceived lower limb weakness in Parkinson’s disease

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Abstract
Background: Lower limb weakness is a long-recognized symptom in patients with Parkinson’s disease (PD), described by James Parkinson in his seminal report on ‘paralysis agitans’. However, little is known on the frequency, clinical correlations, and association with objective decrease in muscle strength in such patients.

Objective: The objective of this study was to assess the frequency of objective and perceived lower limb weakness in patients with PD.

Methods: We studied 90 consecutive patients with PD and 52 age-matched controls. We recorded clinical and demographic variables, as well as perceived weakness and allied abnormal lower limb sensations, including ‘heavy legs’, ‘fatigued legs’, and ‘pain’. Symptoms consistent with restless legs syndrome were not considered. Lower limb strength was determined in both legs by means of the Medical Research Council scale, dynamometric (leg flexion) and weighting machine (leg pressure) measures.

Results: Weakness and allied abnormal lower limb sensations were reported in 69% of patients with PD and 21% of healthy controls. Patients with PD had decreased leg pressure compared with healthy controls ($p = 0.002$). Among patients with PD, an association between perceived leg weakness (and allied sensations) and gait freezing ($p = 0.001$) was observed in the multivariate regression analysis; however, these variables only explained 30.4% of the variance. Moreover, PD patients with and without abnormal lower limb sensations had similar muscle strength by objective measurements.

Conclusion: Perceived lower limb weakness and allied abnormal sensations are common in patients with PD. However, there is a dissociation between perceived weakness and objective muscle strength in the lower limbs. These abnormal sensations were mostly related to gait freezing but a causal association is questionable.

Keywords: gait freezing, muscle strength, neurodegenerative disorders, Parkinson’s disease, weakness

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Introduction
Parkinson’s disease (PD) is a neurodegenerative disorder characterized by degeneration of dopaminergic cells in the substantia nigra with neuronal accumulation of the protein $\alpha$-synuclein; cardinal motor manifestations include bradykinesia, muscle rigidity, tremor, and abnormal postural reflexes. The original term used by James Parkinson to describe this disorder was ‘paralysis agitans’ owing to the perceived decrease in muscle strength and associated tremor. James Parkinson wrote,

The first symptoms perceived are, a slight sense of weakness, with a proneness to trembling . . . one of the legs is discovered slightly to tremble, and is also found to suffer fatigue sooner than the leg of the other side: and in a few months this limb becomes agitated by similar tremblings, and suffers a similar loss of power.
However, by the end of the nineteenth century, J.M. Charcot strongly advocated for the term PD. As the term paralysis agitans was progressively abandoned, few clinical studies focused on muscle strength in PD until the last 20 years, when emerging evidence suggests that muscle weakness is also a prominent feature of PD. A study found decreased muscle strength assessed by objective quantitative measures in parkinsonian and in unaffected extremities in patients with PD. Although frank weakness is usually not detected during physical examination in patients with PD, a previous survey indicated a prevalence of self-perceived weakness in 43.8% of these patients. This figure rivals with reported primary abnormal sensory phenomena, such as tingling, numbness, or pain in 43% of patients with Parkinsonism compared with 8% in control population.

In our experience, patients with PD frequently complain of ‘heavy’ or ‘weak’ legs causing functional impairment for gait. Moreover, as the perceived lower limb weakness in patients with PD is likely multifactorial and not completely explained by objective muscle weakness, we carried out a study to assess the frequency and clinical correlations of perceived and objective lower limb weakness in these patients. We studied muscle strength in patients with PD and healthy controls by clinical and dynamometric methods to assess whether there is a correlation between perceived weakness and objective decrease in muscle strength in the lower extremities.

Materials and methods
We studied consecutive patients diagnosed with PD according to the Queen Square Brain Bank Criteria. Patients were recruited from a movement disorders clinic and evaluated by a neurologist trained in movement disorders. The disease stage was assessed by the Hoehn and Yahr scale. The clinical evaluation was carried out using the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS-III), part III (motor score). The presence of lower limb dyskinesia was also recorded. We also evaluated the presence of perceived orthostatic hypotension (items 1.12) and fatigue (1.13), from the MDS-UPDRS part I. Orthostatic hypotension (OH) was defined as sitting-to-standing systolic blood pressure drop ≥ 20 mmHg or a diastolic blood pressure drop ≥ 10 mmHg. We evaluated the presence of restless legs syndrome (RLS) according to established criteria. The MDS-UPDRS-II, item 2.13, was additionally included as an estimation of the degree of perceived freezing. We additionally evaluated the presence of gait freezing as follows: (1) self-reported (only by the patient); (2) probable (confirmed by a third person); and (3) definitive (observed during the clinical evaluation). The total levodopa equivalent daily dose (LED) at the time of the evaluation was also assessed.

We asked patients and controls whether they perceived lower limb weakness; additionally, we asked for ‘heavy legs’ sensation and ‘fatigued legs’, as these sensations are frequently referred by patients as a form of weakness. We considered all these sensations together as ‘abnormal sensations’. Lower limb pain was also registered, but not included within ‘abnormal sensations’ in the analysis. Patients were asked to rate the abnormal lower limb sensations from 1 (very mild) to 10 (very severe); whether the symptom was symmetric or asymmetric and whether the symptom occurs following physical activity such as walking or occurs at rest. The percentage of the awake day with the symptom (<25%, 25–50%, 51–75%, >75%); and the presence or absence of functional impact which was classified as follows: (1) mild: limitation for long walks > 5 blocks; (2) moderate: limitations for moderate walks, between 2 and 5 blocks; or (3) severe: limitation to walk at all. We studied 52 age-matched, healthy controls. We asked for leg weakness and other abnormal sensations as performed with patients.

We estimated the lower limb strength in patients and healthy controls by three methods: (1) by clinical means using the Medical Research Council (MRC) scale; (2) by dynamometric calculation (ZP-500, Digital Force Gauge, Alipol, China) with partial “leg flexion” (Figure 1(a)) to estimate sustained muscle contractions, and (3) “leg pressure” over the floor using a calibrated weighing machine (BF-679 W, Tanita, Arlington Heights, Illinois, USA) (Figure 1(b)). The latter task was used to examine muscle power as patients needed to generate maximal muscle contraction rapidly to achieve the greatest pressure. For the purpose of reproducibility, we carried out a short intra-rater study, by measuring the lower limb strength by the dynamometer and weighing machine in 14 individuals (patients and controls), at least 2 weeks apart. Differences roughly above 1 kg in all measures were observed, suggesting...
appropriate reproducibility by such methods (Supplementary Table 1). As deconditioning affecting proximal lower limb is a common cause of weakness in PD. The iliopsoas, rectus femoris, sartorius and pectineus were assessed by manual muscle testing as well as handheld dynamometer during thigh flexion. The rectus femoris, vastus lateralis, vastus medialis, and vastus intermedius were assessed during manual test of leg (knee) extension. Hamstrings (biceps femoris, semitendinosus, semimembranosus), gracilis, sartorius, gastrocnemius, and popliteus were assessed during leg pressure. We measured muscle strength by the three methods in 14 patients in the medication ‘Off’ and ‘On’ state. The ‘Off’ state was defined as at least 48 hours without levodopa and any dopaminergic therapy. All patients underwent comprehensive neurological examination, including deep tendon reflexes, and Babinski sign. In case there was evidence of extensive neuropathic changes such as severe motor neuropathy, patients were excluded from the study. We also evaluated the presence of orthostatic hypotension by measuring the blood pressure while seated and 3 minutes after standing.

**Statistics**

Data were summarized in percentages, means, and standard deviations. The paired t test was used to compare means between patients and age-matched controls. The χ² and Fisher’s exact test were used to compare nominal or ordinal data. The likelihood ratio is reported with variables having two or more outcomes. Variables showing statistical significance in the bivariate analysis were included as independent variables in the multivariate logistic regression model using the Wald backward procedure. Dependent variables were ‘abnormal sensations’ and perceived ‘weakness’ in the lower limbs. As statistical interactions were anticipated, among gait freezing by scale item 2.13 (freezing) and item 3.11 (freezing) in the MDS-UPDRS, we considered only the former for statistical multivariate assessment, as that variable yielded most consistent statistically significant differences in the bivariate analysis. Exponentiation of B coefficients (ExpB) were used to provide an estimated weight of the independent variable. We calculated the coefficient of determination (R²) by the Cox and Snell method in the final regression model to assess in what percentage a particular variables predicted the outcome. Goodness of fit for the regression model was evaluated by means of the Hosmer–Lemeshow test; p value <0.05 was considered poor fit. Statistical evaluations were performed using SPSS version 22; a p value < 0.05 was considered significant.

**Results**

**PD patients versus controls**

We studied 92 consecutive patients with PD. Two patients were excluded, one had lumbar stenosis resulting in lower limb weakness, and one had a glioma presenting initially with parkinsonism. We analyzed 90 patients with PD and 52 age-matched normal controls. Sex was equally distributed in both groups. Abnormal lower limb sensations as defined in this study were substantially more common in patients with PD compared with controls: 69% versus 21% (p < 0.001). Perceived ‘weakness’ and ‘heavy legs’ were the most common sensations in patients with PD, whereas ‘fatigued legs’ was the most common complaint in controls (Figure 2). Patients with PD had a higher proportion of asymmetric distribution of abnormal lower
Therapeutic advances in neurological disorders

Limb sensations, and a higher number of patients reported the abnormal sensation present >25% of the awake time compared with controls. Moreover, a higher proportion of patients referred the abnormal sensation to be present at rest. However, the distribution of functional impact determined by walk limitation did not differ between groups (Table 1). Muscle strength did not differ between patients with PD and controls when considering the MRC or dynamometric measure of leg flexion; however, a statistical significant difference was registered regarding leg pressure, as patients with PD had a decrease in muscle strength about 3.5 kg compared with controls \( (p = 0.002) \) (Table 1).

**PD patients with and without abnormal lower limb sensations**

When comparing patients with PD with and without abnormal lower limb sensations, the former had a higher frequency of orthostatic hypotension, fatigue, and gait freezing from the MDS-UPDRS I/II subscores (Table 2). Moreover, the MDS-UPDRS-III subscores related to axial features had higher scores in patients with abnormal lower limb sensations, including hypomimia \( (p = 0.053) \), rising chair \( (p = 0.001) \), gait \( (p = 0.007) \), gait freezing \( (p < 0.001) \), postural stability \( (p = 0.028) \), movement spontaneity \( (p = 0.024) \), and leg bradykinesia \( (p = 0.009, \text{ right}; \ p = 0.007, \text{ left}) \) (Table 2). Total MDS-UPDRS-III score showed a statistical trend \( (p = 0.051) \). Most of these variables showed statistically significance when considering only perceived weakness in the lower limbs, except for orthostatic hypotension, hypomimia, leg bradykinesia, and movement spontaneity (Table 3). Freezing was more frequently observed in PD patients with abnormal lower limb sensations: 25 (40.3%) \textit{versus} 2 (7.14%), \( p = 0.001 \) and in patients with perceived weakness: 21 (46.6%) \textit{versus} 6 (13.3%), \( p = 0.001 \). The leg with more severe abnormal lower limb sensations coincided with the leg with more severe freezing in 23 (92%) of cases. No difference in muscle strength by MRC, leg flexion, and leg pressure were observed, when considering ‘abnormal sensations’ altogether or perceived ‘weakness’ in the lower limbs.

In the multivariate logistic regression analysis, gait freezing by scale and fatigue (item 1.13) were the variables included in the final model, which explained 30.4% of the total variance according to the coefficient of determination (Table 4). If ‘weakness’ is considered as the dependent variable, only gait freezing was included in the final regression model \( (p < 0.001) \). This variable explained 21.1% of the total variance (Table 5).
Table 1. Clinical and demographic features between patients and controls.

| All individuals                  | Parkinson’s disease n = 90 (%) | Healthy controls n = 52 (%) | p value |
|----------------------------------|--------------------------------|-----------------------------|---------|
| Age {years}                      | 68.06 ± 10.24                  | 68.83 ± 8.92                | 0.651   |
| Sex {male}                       | 51 [56.6]                      | 26 [50]                     | 0.442   |
| Abnormal lower limb sensations   | 62 [69]                        | 11 [21]                     | < 0.001 |
| Affected individuals             | n = 62 (%)                     | n = 11 (%)                  |         |
| VAS mean {best – 0 to 10 – worst}| 6.85 ± 2.33                    | 4.09 ± 3.3                  | 0.021   |
| Distribution                     |                                |                             |         |
| Symmetry                         | 22 [35.5]                      | 4 [36.3]                    | 0.012   |
| Asymmetry                        | 38 [61.3]                      | 4 [36.3]                    | LR: 6.41 [0.040] |
| Unclear                          | 2 [3.2]                        | 3 [27.2]                    |         |
| Percentage awake                 |                                |                             |         |
| <25%                             | 11 [17.7]                      | 8 [72.7]                    | 0.002   |
| 25–50%                           | 15 [24.2]                      | 1 [9]                       | LR: 14.29 [0.006] |
| 51–75%                           | 9 [14.5]                       | 1 [9]                       |         |
| >75%                             | 27 [43.5]                      | 1 [9]                       |         |
| Occurs after physical activity   |                                |                             |         |
| No                               | 47 [75.8]                      | 4 [36.3]                    | 0.001   |
| Occasionally                     | 6 [9.7]                        | 6 [54.5]                    | LR: 10.7 [0.005] |
| Always                           | 9 [14.5]                       | 1 [9]                       |         |
| Functional impact                |                                |                             |         |
| No                               | 8 [12.9]                       | 3 [27.2]                    | 0.257   |
| Mild                             | 12 [19.3]                      | 4 [36.3]                    | LR: 3.93 [0.268] |
| Moderate                         | 28 [45.1]                      | 3 [27.2]                    |         |
| Severe                           | 14 [22.5]                      | 1 [9.1]                     |         |
| Total                            | 54 [87]                        | 8 [72.1]                    |         |
| Muscle strength {MRC}            |                                |                             |         |
| Right leg                        |                                |                             |         |
| Proximal                         | 4.80 ± 0.40                    | 4.90 ± 0.90                 | 0.082   |
| Distal                           | 4.93 ± 0.25                    | 4.96 ± 0.19                 | 0.486   |
| Ankle                            | 5.00 ± 0.0                     | 4.98 ± 0.14                 | 0.322   |
| Left leg                         |                                |                             |         |
| Proximal                         | 4.80 ± 0.40                    | 4.90 ± 0.30                 | 0.082   |
| Distal                           | 4.91 ± 0.28                    | 4.96 ± 0.19                 | 0.215   |

(Continued)
Table 1. (Continued)

| All individuals | Parkinson’s disease with abnormal lower limb sensations \( n = 62 \) (%) | Healthy controls \( n = 52 \) (%) | \( p \) value |
|------------------|-------------------------------------------------|---------------------------------|-------------|
| Ankle            | \( 5.00 \pm 0.0 \)                              | \( 4.98 \pm 0.14 \)              | 0.322       |
| Muscle strength (leg flexion, kg) | | | |
| Right leg       | \( 14.21 \pm 2.75 \)                            | \( 14.38 \pm 3.09 \)              | 0.762       |
| Left leg        | \( 13.80 \pm 2.85 \)                            | \( 14.13 \pm 3.30 \)              | 0.578       |
| Muscle strength (leg pressure, kg) | | | |
| Right leg       | \( 12.31 \pm 4.70 \)                            | \( 15.87 \pm 4.89 \)              | 0.002       |
| Left leg        | \( 12.05 \pm 4.90 \)                            | \( 15.67 \pm 7.19 \)              | 0.002       |

LR, log ratio; MRC, Medical Research Council; VAS, Visual Analog Scale.

Table 2. Clinical and demographic features between patients with and without abnormal lower limb sensations.

|                      | Parkinson’s disease with abnormal lower limb sensations \( n = 62 \) (%) | Parkinson’s disease without abnormal lower limb sensations \( n = 28 \) (%) | \( p \) value |
|----------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-------------|
| Age (years)          | \( 69.02 \pm 10.6 \)                                            | \( 65.93 \pm 9.18 \)                                            | 0.187       |
| Sex (male)           | \( 34 \) [54.8]                                                 | \( 17 \) [60.7]                                                 | 0.603       |
| RLS                  | \( 3 \) [4.8]                                                   | \( 1 \) [3.6]                                                   | 1.000       |
| Receiving levodopa   | \( 45 \) [72.5]                                                 | \( 15 \) [53.6]                                                 | 0.127       |
| LEDD                 | \( 705.4 \pm 653.1 \)                                           | \( 508.6 \pm 493.8 \)                                           | 0.159       |
| Hoehn-Yahr stage     | \( 3.42 \pm 0.96 \)                                             | \( 3.21 \pm 2.40 \)                                             | 0.205       |
| MDS-UPDRS-II subscores (item) | | | |
| Orthostatic hypotension (1.12) | \( 1.02 \pm 1.20 \) | \( 0.50 \pm 0.83 \) | 0.022 |
| Fatigue (1.13)       | \( 1.79 \pm 1.08 \)                                             | \( 0.96 \pm 1.10 \)                                             | 0.001       |
| Gait freezing (2.13) | \( 2.16 \pm 1.38 \)                                             | \( 0.71 \pm 1.18 \)                                             | <0.001      |
| MDS-UPDRS-III subscores (item) | | | |
| Language             | \( 1.0 \pm 1.02 \)                                              | \( 0.61 \pm 1.03 \)                                             | 0.096       |
| Facial expression    | \( 1.02 \pm 0.93 \)                                             | \( 0.61 \pm 0.87 \)                                             | 0.053       |
| Leg rigidity composite score (3.3) | \( 1.60 \pm 0.96 \) | \( 1.48 \pm 0.87 \) | 0.568 |
| Leg bradykinesia composite score | | | |
| Right (3.7 & 3.8)    | \( 1.30 \pm 0.98 \)                                             | \( 0.73 \pm 0.78 \)                                             | 0.009       |
| Left (3.7 & 3.8)     | \( 1.62 \pm 0.98 \)                                             | \( 1.03 \pm 0.81 \)                                             | 0.007       |
| Rising chair (3.9)   | \( 1.21 \pm 1.30 \)                                             | \( 0.36 \pm 0.55 \)                                             | 0.001       |

(Continued)
Table 2. (Continued)

|                          | Parkinson’s disease with abnormal lower limb sensations n = 62 (%) | Parkinson’s disease without abnormal lower limb sensations n = 28 (%) | p value |
|--------------------------|------------------------------------------------------------------|------------------------------------------------------------------|---------|
| Gait (3.10)              | 2.03 ± 1.08                                                       | 1.36 ± 1.02                                                       | 0.007   |
| Gait freezing (3.11)     | 1.06 ± 1.50                                                       | 0.14 ± 0.59                                                       | < 0.001 |
| Postural stability (3.12)| 1.81 ± 1.12                                                       | 1.25 ± 1.00                                                       | 0.028   |
| Posture (3.13)           | 1.37 ± 0.92                                                       | 0.89 ± 0.83                                                       | 0.022   |
| Movement spontaneity (3.14)| 1.03 ± 0.94                                                      | 0.56 ± 0.80                                                       | 0.024   |
| Leg rest tremor composite score (3.17) | 0.31 ± 0.63                                                      | 0.39 ± 0.74                                                       | 0.572   |
| MDS-UPDRS-III total score| 37.06 ± 16.5                                                      | 29.86 ± 14.8                                                      | 0.051   |
| Orthostatic hypotensiona |                                                                  |                                                                 |         |
| No                       | 36 (58)                                                          | 13 (46.4)                                                        | 0.554   |
| Mild                     | 17 (27.4)                                                        | 9 (32.1)                                                         | LR: 1.17 (0.557) |
| Fulfills criteria        | 9 (14.5)                                                         | 6 (21.4)                                                         |         |
| Gait ‘freezing’ scale    |                                                                  |                                                                 |         |
| 0 None                   | 8 (12.9)                                                         | 20 (71.4)                                                        | < 0.001 |
| 1 Reported by the patient| 9 (14.5)                                                         | 3 (10.7)                                                         | LR: 32.1 (<0.001) |
| 2 Observed by a witness  | 17 (27.4)                                                        | 2 (7.14)                                                         |         |
| 3 Observed during physical exam | 28 (45.1)                                                       | 3 (10.7)                                                         |         |
| Muscle strength (MRC)    |                                                                  |                                                                 |         |
| Right/left leg           |                                                                  |                                                                 |         |
| Proximal                 | 4.76 ± 0.43                                                      | 4.89 ± 0.31                                                      | 0.100   |
| Distal                   | 4.92 ± 0.27                                                      | 4.96 ± 0.19                                                      | 0.371   |
| Ankle                    | 5.0 ± 0.0                                                        | 5.0 ± 0.0                                                        | 1.000   |
| Muscle strength (leg flexion, kg) |                                                              |                                                                 |         |
| Right leg                | 14.00 ± 2.78                                                     | 14.73 ± 2.67                                                     | 0.359   |
| Left leg                 | 13.37 ± 2.80                                                     | 14.90 ± 2.74                                                     | 0.060   |
| Muscle strength (leg pressure, kg) |                                                              |                                                                 |         |
| Right leg                | 11.99 ± 4.60                                                     | 12.98 ± 4.93                                                     | 0.360   |
| Left leg                 | 11.47 ± 4.89                                                     | 13.27 ± 4.78                                                     | 0.110   |

LEDD, Levodopa Equivalent Daily Dose; LR, log ratio; MRC, Medical Research Council; RLS, restless legs syndrome. OH is defined as drop in systolic blood pressure ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg. Mild OH was classified if drop in systolic blood pressure was between 10 and 19 mmHg and/or diastolic blood pressure drop between 5 and 9 mmHg.
### Table 3. Clinical and demographic features between patients with and without perceived lower limb weakness.

|                                      | Parkinson’s disease with perceived lower limb weakness n = 45 (%) | Parkinson’s disease without perceived lower limb weakness n = 45 (%) | p value |
|--------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------|---------|
| Age (years)                          | 69.98 ± 10.43                                                    | 66.13 ± 9.78                                                     | 0.075   |
| Sex (male)                           | 29 [64.4]                                                        | 22 [48.8]                                                        | 0.136   |
| RLS                                  | 2 [4.4]                                                          | 2 [4.4]                                                          | 1.000   |
| Receiving levodopa                   | 32 [71.1]                                                        | 29 [64.4]                                                        | 0.499   |
| LEDD                                 | 706 ± 637                                                        | 581 ± 586                                                        | 0.334   |
| Hoehn-Yahr stage                     | 3.51 ± 0.95                                                      | 3.20 ± 1.97                                                      | 0.343   |
| MDS-UPDRS-II subscores               |                                                                 |                                                                 |         |
| Orthostatic hypotension [item 1.12]  | 0.91 ± 1.10                                                      | 0.80 ± 1.16                                                      | 0.543   |
| Fatigue [item 1.13]                  | 1.98 ± 1.17                                                      | 1.09 ± 0.95                                                      | < 0.001 |
| Gait freezing [item 2.13]            | 2.40 ± 1.38                                                      | 1.02 ± 1.23                                                      | < 0.001 |
| MDS-UPDRS-III subscores              |                                                                 |                                                                 |         |
| Language                             | 1.04 ± 1.06                                                      | 0.71 ± 0.99                                                      | 0.128   |
| Facial expression                    | 1.0 ± 0.95                                                       | 0.78 ± 0.90                                                      | 0.259   |
| Leg rigidity composite score [3.3]   | 1.55 ± 0.94                                                      | 1.57 ± 0.95                                                      | 0.911   |
| Leg bradykinesia composite score     |                                                                 |                                                                 |         |
| Right [3.7 & 3.8]                    | 1.25 ± 1.03                                                      | 0.98 ± 0.88                                                      | 0.191   |
| Left [3.7 & 3.8]                     | 1.59 ± 0.99                                                      | 1.29 ± 0.92                                                      | 0.141   |
| Rising chair [3.9]                   | 1.31 ± 1.34                                                      | 0.58 ± 0.89                                                      | 0.003   |
| Gait [3.10]                          | 2.16 ± 1.09                                                      | 1.49 ± 1.03                                                      | 0.004   |
| Gait freezing [3.11]                 | 1.24 ± 1.58                                                      | 0.31 ± 0.87                                                      | 0.001   |
| Postural stability [3.12]            | 1.91 ± 1.18                                                      | 1.36 ± 0.98                                                      | 0.017   |
| Posture [3.13]                       | 1.49 ± 0.92                                                      | 0.96 ± 0.85                                                      | 0.005   |
| Movement spontaneity [3.14]          | 0.93 ± 0.86                                                      | 0.84 ± 0.99                                                      | 0.639   |
| Leg rest tremor composite score [3.17]| 0.23 ± 0.58                                                      | 0.43 ± 0.73                                                      | 0.156   |
| MDS-UPDRS-III total score            | 36.53 ± 16.5                                                    | 33.1 ± 16.0                                                      | 0.321   |
| Orthostatic hypotension              |                                                                 |                                                                 |         |
| No                                   | 26 [57.7]                                                        | 23 [51.1]                                                        | 0.817   |
| Mild                                 | 12 [26.6]                                                        | 14 [31.1]                                                        | LR 0.465 |

(Continued)
**Table 3.** (Continued)

| | Parkinson's disease with perceived lower limb weakness | Parkinson's disease without perceived lower limb weakness | \( p \) value |
|---|---|---|---|
| Fulfills criteria | 7 (15.5) | 8 (17.8) | 0.817 |
| Gait ‘freezing’ scale | | | |
| 0 None | 6 (13.3) | 22 (48.9) | <0.001 |
| 1 Reported by the patient | 3 (6.7) | 9 (20) | LR 23.7 |
| 2 Observed by a witness | 13 (28.9) | 6 (13.3) | (<0.001) |
| 3 Observed during physical exam | 23 (51.1) | 8 (17.8) | |

**Muscle strength (MRC)**

| | Proximal | Distal | Ankle |
|---|---|---|---|
| Right/left leg | | | |
| Right leg | 4.76 ± 0.43 | 4.84 ± 0.37 | 0.297 |
| Left leg | 4.93 ± 0.25 | 4.93 ± 0.25 | 1.000 |
| Muscle strength (leg flexion, kg) | | | |
| Right leg | 14.21 ± 2.55 | 14.21 ± 2.96 | 1.000 |
| Left leg | 13.39 ± 2.75 | 14.19 ± 2.92 | 0.277 |

**Muscle strength (leg pressure, kg)**

| | Right leg | Left leg |
|---|---|---|
| Right leg | 12.51 ± 4.73 | 12.13 ± 4.71 | 0.709 |
| Left leg | 11.92 ± 4.88 | 12.17 ± 4.96 | 0.811 |

| | \( \text{LEDD, Levodopa Equivalent Daily Dose; MRC, Medical Research Council; RLS, restless legs syndrome.} \) |

**PD patients in the medication ‘Off’ and ‘On’ state**

When comparing muscle strength: leg flexion and leg pressure in the medication ‘Off’ and ‘On’ state, a difference below 500 gr was recorded in all cases, except for right leg pressure (about 2 kg); we consider these differences relatively minor, suggesting that the motor status (On versus Off) does not have a major influence in the objective measures of muscle strength in the lower limbs. The total MDS-UPDRS-III scores were statistically significant between the medication ‘Off’ versus ‘On’ state: 39.73 versus 16.64 (\( p < 0.001 \)) (Supplementary Table 2).

**Table 4.** Multivariate analysis of statistically significant variables in the bivariate analysis.

| Variables in the final equation | \( \text{Exp}^b \) coefficient | \( \text{Exp}^b \) 95% CI | \( p \) value |
|---|---|---|---|
| Gait freezing (by scale) | 2.826 | 1.696–4.707 | <0.001 |
| Fatigue (Item 1.13) | 1.597 | 0.929–2.744 | 0.090 |
| Constant | 0.320 | | 0.022 |

CI, confidence interval.

Constant: B = 1.139, \( \text{Exp}^b = 0.320, p = 0.022 \). Hosmer–Lemeshow: \( p = 0.209 \). Variables not included in the final equation: LL, bradykinesia; item 1.12, raising chair; gait, postural stability, posture, spontaneous movements. Cox and Snell \( R^2 \) for the final model: 0.304.
Discussion

There are several findings related to this study. We corroborate that perceived weakness and allied abnormal sensations in the lower extremities are much more prevalent in patients with PD than in age-matched healthy controls (69% versus 21%), similar to other studies.6 Those sensations did not correspond to RLS. These abnormal sensations were not consistent with peripheral neuropathy or small fiber sensory neuropathy, although skin biopsies were not carried out in this study.14 There were several qualitative differences between PD patients and controls related to the abnormal sensations in the lower limbs. Individuals with PD rated their lower limb sensations as more severe; distribution was mostly asymmetric, occurred mainly at rest and lasted longer throughout the day compared with controls. However, the functional impact did not differ between groups (Table 1). These differences suggested a different underlying pathophysiology in such abnormal sensations in patients compared with controls.

We also compared PD patients with and without abnormal lower limb sensations. Several parkinsonian features showed higher scores in patients complaining of lower limb weakness and allied abnormal sensations, suggesting a clinical association; particularly axial features, such as hipomimia, rising from chair, gait, posture and gait freezing, but also lower limb bradykinesia, and non-motor features such as fatigue and orthostatic hypotension. The multivariate regression to control for independent variables showed that gait freezing is mainly associated with perceived weakness and allied abnormal lower limb sensations. It is unclear, however, whether there is a causal association between freezing and perceived weakness, as gait freezing is a manifestation occurring during muscle activation while perceived weakness occurs mainly at rest. This suggests that they may not be causally related but rather follow a common abnormality in motor processing or brain’s connectivity,15 a consideration supported by the relatively low coefficient of determination (R²) for perceived weakness (21.1%) and allied abnormal lower limb sensations altogether (30.4%).

Abnormal sensory processing, such as reduced thresholds in thermal, electrical, cold, or mechanical pain, and abnormal activation of cortical pain-related areas with nociceptive stimuli have been observed in patients with PD and are consistent with a hypersensitivity state.16,17 A proprioceptive deficit in PD has been related with axial abnormalities such as static and dynamic postural control,18,19 suggesting a link between abnormalities in sensory processing and motor dysfunction in patients with PD. These abnormalities may be related to degeneration of dopaminergic and non-dopaminergic pathways (noradrenergic, cholinergic, and serotoninergic) and they have been used to explain the high frequency of pain in PD,19 but may also be implicated in the pathogenesis of other sensory phenomena including perceived weakness. The asymmetry of perceived lower limb weakness more commonly occurring in the leg with more severe freezing and the presence of these abnormal sensations at rest suggest an abnormality in sensory processing where dopaminergic pathways in basal ganglia may be implicated.20 In addition, the role of non-dopaminergic mechanisms is supported by the inconsistent response of abnormal sensations to these medications, such as pain improvement with levodopa.

In our study, we found no difference in muscle strength by clinical examination, using MRC, between patients and controls. However, muscle strength was reduced in PD patients compared with controls when assessed by leg pressure, but not by leg flexion, which tests sustained muscle contractions (Table 1). Leg pressure requires rapid muscle contractions (velocity) to achieve
maximal muscle strength (force). Muscle power (force \times velocity) has been found decreased in PD. An early study assessing elbow extensor torque suggested that decreased strength in PD is related to a decreased ability to generate rapid muscle contractions.\textsuperscript{21} This observation was supported by reports of greater muscle weakness in PD patients when performing isokinetic muscle contractions at increasing velocities.\textsuperscript{22,23} Such difference may be influenced by progressive bradykinesia as the disease progresses.\textsuperscript{25} However, more recent evidence suggests that muscle weakness in hip and knee flexors or extensors exists in patients with PD, compared with age-matched controls, independently of bradykinesia.\textsuperscript{24} In this instance, bradykinesia plays a role;\textsuperscript{25} but decreased muscle strength seems to be the major contributor of reduced muscle power in PD.\textsuperscript{26} In summary, objective assessment of muscle strength in our study showed that PD patients have decreased leg pressing which requires rapid and strong muscle contractions, but not abnormal muscle resistant which is in accordance with previous reports.

However, none of the methods we used to assess for muscle strength differed between patients with and without perceived lower limb weakness and allied sensations. Moreover, no differences in muscle strength were observed in the medication ‘On’ and ‘Off’ state. This finding suggests a dissociation between perceived weakness and actual muscle strength or power in patients with PD. Dopaminergic therapy, however, may influence perceived lower limb weakness. For example, levodopa can improve gait freezing in most patients with PD but make it worse in few cases;\textsuperscript{27} this may theoretically improve or worsen perceived lower limb weakness, respectively. Moreover, dopaminergic therapy may improve mobility; this may secondarily lead to decreased muscle wasting, less muscle contractures, and improved muscle tone, potentially leading to less perceived muscle weakness. In this instance, muscle resistant exercises may provide benefit in perceived muscle weakness. Further studies should clarify the effects of exercise and dopaminergic medication in objective and perceived muscle weakness and verify whether the medication ‘On’ state improves objective muscle strength in such cases.

The origin of muscle weakness in PD is unclear. A central component has been postulated following the observation that there is a positive correlation between quadriceps muscle weakness and higher UPDRS motor scores; moreover, severely affected PD patients show higher activation deficits and higher antagonist moments compared with less affected PD patients or controls.\textsuperscript{28,29} Identification of lower limb weakness is important in clinical practice, as it seems to contribute to decreased hip bone mineral density in females with PD.\textsuperscript{30} It is unclear, however, whether this also occurs in males with PD. Moreover, decreased lower limb strength seems more common in patients with the Postural Instability Gait Disorder (PIGD) subtype of PD\textsuperscript{31} which is related to slower walking velocity, poorer balance, and increased risk of multiple falls.\textsuperscript{25,32}

Our study has limitations, for example, we did not record all possible abnormal sensation in the lower limbs; however, the frequency of abnormal sensations is remarkably similar to a previous study carried out in the 1970s.\textsuperscript{6} It is unclear whether the methods used to assess muscle strength are optimal; however, we chose these methods as they are easy to replicate and use in clinical practice and have low observation-bias. However, several limitations have been highlighted for manual testing of muscle strength, including a ceiling and floor effects as well as high interrater variability.\textsuperscript{33} For that reason, alternative methods have been proposed such as own weight bearing, including single limb heel raise test.\textsuperscript{34} In our study, we did not find statistically significant difference between MRC patients with PD and controls. Moreover, some used scales such as rating of severity of abnormal lower limb weakness, functional impact, and percentage of awake time are not based on validated scales; however, they are easy to use in clinical practice and likely easy to replicate owing to their simplicity. We acknowledge that it is unclear whether sensations such as ‘heavy’ or ‘fatigued’ legs are proxy for perceived weakness; however, the statistical analysis including all these abnormal sensations showed similar results that when only ‘weakness’ was considered, therefore we believe they should be considered altogether.

Concluding remarks
Lower limb weakness and allied abnormal sensations are a common but largely neglected manifestation in PD. These abnormal sensations were more common in patients with greater lower limb bradykinesia, fatigue, orthostatic hypotension and
various axial symptoms; however, only gait freezing showed a consistent association when controlling for other independent variables, suggesting a common underlying central abnormality for both phenomena. Although PD patients showed decreased muscle strength as originally described by J. Parkinson, this phenomenon was not associated with perceived muscle weakness and allied manifestations, suggesting a dissociation between subjective and objective muscle strength. Further studies should clarify the neurophysiological basis of perceived lower limb weakness, biomechanical aspects of muscle weakness, and impact in functional mobility in patients with PD. In the meantime, adjustment in dopaminergic therapy and muscle resistant exercises may be attempt.

**Declarations**

**Ethics approval and consent to participate**
The study was approved by the local committee of ethics at Sante Medical Tower (number: 20220501), and patients and controls provided written informed consent to participate in the study.

**Consent for publication**
Not applicable.

**Author contributions**

**Marlene Alonso-Juarez**: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Software; Writing – original draft.

**Robert Fekete**: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – review & editing.

**José Fidel Baizabal- Carvallo**: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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**Supplemental material**
Supplemental material for this article is available online.

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