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Original article

Clinical effects of robot-assisted gait training and treadmill training for Parkinson's disease. A randomized controlled trial

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ABSTRACT

Background: Although gait disorders strongly contribute to perceived disability in people with Parkinson's disease, clinical trials have failed to identify which task-oriented gait training method can provide the best benefit. Freezing of gait remains one of the least investigated and most troublesome symptoms.
Objective: We aimed to compare the effects of robot-assisted gait training and treadmill training on endurance and gait capacity in people with Parkinson disease; the secondary aim was to compare the effect of the treatments in people with freezing and/or severe gait disability and assess changes in overall disease-related disability and quality of life.
Methods: Outpatients with Parkinson disease (Hoehn and Yahr stage ≥ 2) were randomly assigned to receive 20 sessions of 45-min gait training assisted by an end-effector robotic device (G-EO System) or treadmill training. Outcome assessments were the 6-min walk test, Timed Up and Go test, Freezing of Gait Questionnaire, Unified Parkinson's Disease Rating Scales and Parkinson's Disease Quality of Life Questionnaire-39 administered before (T0) and after treatment (T1).
Results: We included 96 individuals with Parkinson disease: 48 with robot-assisted gait training and 48 treadmill training. Both groups showed significant improvement in all outcomes. As compared with baseline, with robot-assisted gait training and treadmill training, endurance and gait capacity were enhanced by 18% and 12%, respectively, and motor symptoms and quality of life were improved by 17% and 15%. The maximum advantage was observed with the Freezing of Gait Questionnaire score, which decreased by 20% after either treatment. On post-hoc analysis, dependent walkers benefited more than independent walkers from any gait training, whereas freezers gained more from robot-assisted than treadmill training in terms of freezing reduction.
Conclusions: Repetitive intensive gait training is an effective treatment for people with Parkinson disease and can increase endurance and gait velocity, especially for those with severe walking disability. Advantages are greater with robot-assisted gait training than treadmill training for individuals with freezing of gait – related disability.

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1. Introduction

The management of gait problems is one of the main goals of rehabilitation for people with Parkinson disease (pwPD) [1,2]. In the early stage of the disease, pwPD show reduced walking speed and stride length, with increased cadence, double limb support and gait rhythm disruption [2,3]. The disease progression is characterized by the onset of disabling axial symptoms such as postural instability and freezing of gait (FOG), which are poorly sensitive to pharmacological therapy based on modulation of dopaminergic pathways [2,4]. Hence, additional interventions to improve the gait of pwPD are needed.

Systematic reviews and guidelines confirmed physical therapy as an effective strategy to improve gait, overall physical functioning and quality of life of pwPD [5–7]. The aim of physiotherapy is to help individuals maintain their maximum level of mobility, activity and independence. Gait training with electromechanical devices, such as a treadmill, was found effective for pwPD [5–8]. Treadmill training (TT) allows people to practice gait with a higher speed and greater step length than with over-ground training. These exercise features provided a better outcome in pwPD with minimal to moderate disability [5] when considering gait capacity, with no significant improvement in endurance. Although TT is widely available for both inpatients and outpatients in industrialized countries, its greater value as compared with traditional training cannot be generalized to more disabled or older individuals [5].

Recently, robot-assisted gait training (RAGT) devices have been increasingly used in rehabilitation protocols for pwPD [9–20]. The rationale behind the use of RAGT is the opportunity to additionally treat individuals with severe axial disorders and to increase the training challenge, by imposing specific kinematic parameters and providing continuous intensive stereotyped somatosensory cues. In the last 5 years, the feasibility, acceptability and safety of RAGT were tested and positively appraised in pwPD. Nevertheless, no clinical trial has determined whether RAGT is preferred to the less expensive TT in pwPD, according to disease stage or specific clinical indications (Table 1) [3,9–20]. Particularly, no controlled study has determined the superiority of approaches such as RAGT or TT on drug-resistant (or poorly responsive) gait disorders such as FOG [6,7].

The main aim of this study was to compare the effects of RAGT (G-EO system) and TT on endurance and gait capacity in a large sample of pwPD with mild to severe gait disability. The secondary aim was to compare the effect of the treatments in subgroups with different gait profiles and define their impact on overall disease-related disability and quality of life.

2. Methods

2.1. Study design

This was a multicenter single-blind prospective randomized controlled study of the efficacy of RAGT compared to TT in pwPD. The study was carried out in 3 neurorehabilitation facilities with staff and resources dedicated to the rehabilitation of pwPD.

2.2. Participants

Individuals with idiopathic PD consecutively referred for counseling and outpatient rehabilitation management were included if they:

- had a diagnosis of idiopathic PD by UK Brain Bank criteria;
- had Hoehn and Yahr stage ≥ 2;
- were 50 to 80 years old;
- could stand upright for at least 20 min, independently or with assistance;
- had disease-related walking difficulty (i.e., Unified Parkinson's Disease Rating Scale [UPDRS] part II, item 15 = 1–3);
- could walk for 10 m independently or with assistance;
- had stable symptomatic medications during the month before enrolment and;
- provided written informed consent.

We excluded individuals with:

- an inability to understand study instructions (Informed Consent Test of Comprehension);
- cognitive impairment (Mini Mental State Examination score [MMSE] < 24);
- alcohol or drug abuse (including dopamine dysregulation syndrome), active depression, anxiety or psychosis interfering with the use of the equipment or testing;
- coexisting disabling neurological or orthopedic disorders;
- previous brain surgery (including pallidotomy, thalamotomy or deep brain stimulation);
- cardiovascular or lung disease potentially affecting tolerance to intensive training and;
- participation in other trials in the last 6 months.

Block randomization was used to allocate participants to 2 groups defined as RAGT and TT. A stratification approach was used to allow a balanced between-group distribution of participants enrolled at each center, with respect to the main independent variables. Age, sex, disease duration and Hoehn and Yahr stage were controlled as confounding factors when participants were assigned to the study groups. Allocation to treatment was concealed and based on a customized purpose-built software.

2.3. Rehabilitation interventions

2.3.1. RAGT group

Each participant completed 20 sessions (5 days/week for 4 weeks) of RAGT with the end-effector robotic device G-EO system (Reha Technology AG; Olten, Switzerland). The practice consisted in a robot-assisted walking at variable speeds for 45 min, exploiting partial body weight support (BWS). At the first session, all participants started with 30% to 40% BWS at 1.5 km/h. The speed was progressively increased to reach 2.2 to 2.5 km/h maximum, and BWS was gradually decreased up to 20% according to tolerance. During training, a physiotherapist supervised individuals to assist them if necessary. The total steps taken during the simulated walking were converted to the distance covered based on the step length previously set as 0.5 m normalized to the participant's height.

2.3.2. TT group

Each participant performed 20 sessions (5 days/week for 4 weeks) of TT (Runner EE 720 MTR and Runner RUN2011, Modena, Italy) without BWS. Participants were instructed to walk on treadmill for 45 min. At the beginning of each session, the walking speed was set at 0.8 to 1 km/h and gradually increased to 2.0 km/h or higher depending on tolerance. During training, the physiotherapist supervised the individual by standing to the side of treadmill device.

2.4. Exercise intensity

To allow for treatment comparability, exercise parameters were recorded at each session. In particular, heart rate and blood pressure were recorded at the beginning and the end of each

Table 1
Studies reporting the efficacy of robot-assisted gait training (RAGT) in people with Parkinson disease.

Authors	Study design	Sample no.	RAGT device and treatment protocol	Control	Clinical outcome measures	Instrumental gait assessment (spatial-temporal parameters)	Follow-up	Main findings
Lo et al., 2010 [10]	Pilot Case study	4	Lokomat 10 sessions, 30 min, 2/week, 5 weeks	None	FOG-Q, FOG and falls diary, a clinician-rated video FOG score, Posture and Gait Score from UPDRS items 13–15, 29–30, PDQ-39	GAITRite Mat, CIR systems	None	Decrease in FOG events Improvement in all clinical and instrumental measures
Ustinova et al., 2011 [9]	Case study	1	Lokomat 6 sessions, 45 min, 2 weeks	None	UPDRS	Flock of birds' motion analysis system	15 weeks	Improvement in both clinical and gait instrumental measures. Results partially maintained at follow-up
Picelli et al., 2012 [29]	RCT	36	Gait trainer 12 sessions, 45 min, 3/week, 4 weeks	PT	10MWT, 6MWT, UPDRS, PFS	GAITRite Systems	1 month	RAGT induces a greater improvement than PT in 10MWT, stride length, cadence, fatigue and UPDRS maintained at follow-up
Picelli et al., 2012 [13]	RCT	34	Gait trainer GT1 12 sessions, 40 min, 3/week, 4 weeks	PT	10MWT, TUG, BBS, Nutt's rating, ABC, UPDRS III	None	1 month	RAGT induced a greater improvement in all outcome measures both after treatment and at 1-month follow-up
Sale et al., 2013 [3]	Pilot RCT	20	G-EO system device 20 sessions, 45 min, 5/week, 4 weeks	TT	UPDRS III	3D gait analysis, ELITE2002, BTS, Italy	None	RAGT induced a greater improvement in spatio-temporal parameters
Picelli et al., 2013 [19]	RCT	60	Gait trainer GT1 12 sessions, 45 min, 4 weeks	1) TT without body weight support 2) PT	10MWT, 6MWT, BBS, UPDRS, PFS	GAITRite systems	3 months	10MWT, 6MWT, stride length: significant improvement favouring the RAGT and TT vs. PT BBS: significant difference between RAGT vs. PT and TT at T1 (after treatment) and RAGT vs. PT at T2 Parkinson's Fatigue Scale and UPDRS: significant difference between RAGT vs. PT at both T1 and T2
Barbe et al., 2013 [11]	Pilot case study	3	Lokomat 10–12 sessions, 30 min	None	FOG-Q, UPDRS	Leonardo Gangway mechanograph	6 week	Improvement in all outcome measures At follow-up: FOG-Q still better than at baseline
Nardo et al., 2014 [20]	Case series	9	Lokomat 45 min, every days, 5 weeks	None	UPDRS III	Elite Clinic, BTS Bioengineering, Milan, Italy	None	RAGT improved all the spatio-temporal gait parameters, UPDRS III and gait subscore
Picelli et al., 2015 [22]	RCT	66	Gait trainer GT1	Conventional balance training	TUG, BBS, ABC, UPDRS	None	1 month	No significant between-group differences

Table 1 (*Continued*)

Authors	Study design	Sample no.	RAGT device and treatment protocol	Control	Clinical outcome measures	Instrumental gait assessment (spatial-temporal parameters)	Follow-up	Main findings
			12 sessions, 45 min, 3/week, 4 weeks					
Pilleri et al., 2015 [17]	Open-label non-controlled study	18	Gait Trainer GT	None	FOG-Q, 10MWT, TUG, 360° narrow turns, FFES, BBS, UPDRS II and III, PDQ-8	None	None	Improvement in all measures except UPDRS III
			15 sessions, 30 min, 5/week, 3 weeks					
Carda et al., 2015 [14]	RCT	30	Lokomat	TT	6MWT, 10MWT, TUG, UPDRS III, SF-12 PCS, SF-12 MCS	None	3 and 6 months	RAGT was not superior to TT
			12 sessions, 30 min, 3/week, 4 weeks					
Galli et al., 2016 [16]	RCT	50	G-EO system device	TT	UPDRS III	3D Gait analysis, ELITE2002, BTS, Italy	None	RAGT improved spatio-temporal p arameters of gait and proximal level gait kinematics. UPDRS III improved in both RAGT and TT groups
			20 sessions, 45 min, 5/week, 4 weeks					
Furnari et al., 2017 [15]	RCT	38	Lokomat + conventional exercise program	Conventional gait training + conventional exercise program	10MWT, Tinetti Test, UPDRS III, PDQ-39, GDS	None	12 weeks	Tinetti Test and UPDRS III scores improved in both groups. At follow-up: the gain was maintained only in the RAGT
			24 session, 60 min, 6/week, 4 weeks					

ABC: Activities-Specific Balance Confidence scale; BBS: Berg Balance Scale; FFES: Fear of Falling Efficacy Scale; FOG-Q: Freezing of Gait Questionnaire; GDS: Geriatric Depression Scale; 10MWT: 10-m walking test; 6MWT: 6-min walk test; PDQ-8: Parkinson's Disease Questionnaire-8; PDQ-39: Parkinson's Disease Questionnaire-39; PFS: Parkinson Fatigue Scale; PT: physical therapy; RAGT: robot-assisted gait training; RCT: randomized controlled trial; SF-12 PCS: Physical Health Composite Score of the Medical Outcomes Study Short Form 12; SF-12 MCS: Mental Health Composite Score of the Medical Outcomes Study Short Form 12; TT: treadmill training; TUG: Timed Up and Go test; UPDRS: Unified Parkinson's Disease Rating Scale. In all studies, the participants were assessed and treated in ON medication state.

session; moreover, heart rate was monitored continuously during training with a finger pulse oximeter. Total training duration and intensity were based on a prudent approach, assuming that heart rate should neither exceed 120 beats/min (bpm) nor fall below 100 bpm. We calculated this limit by using the Karnoven formula, with maximum heart rate obtained by subtracting the participant's age from 220 and assuming a resting heart rate of 70 bpm. Training was always performed under the effect of chronic anti-parkinsonian therapy (i.e., in the best motor condition ["ON" phase]).

Participants in both groups were excluded from the study if they missed one session without redoing the session or interrupted treatment for more than 3 consecutive days.

2.5. Outcome assessment

The primary endpoint of the study was the change in endurance measured by the 6-min Walk Test (6MWT) [21]. Changes in gait capacity, measured by the Time Up and Go test (TUG) and 10-m Walk Test (10MWT) [22], FOG-Questionnaire (FOG-Q) [23,24], and the UPDRS II item 14, were investigated. Among secondary outcomes, walking performance was assessed by FOG measures (FOG-Q [23,24] and UPDRS II item 14) and the Walking Handicap Scale (WHS) [25]; overall and selective disease-related disability were assessed by the total UPDRS and subtotal UPDRS part II and III scores [26]; quality of life was measured by the Parkinson's Disease Questionnaire-39 (PDQ-39) [27].

All outcome measures were collected in the "ON medication" phase (i.e., 1 h after oral consumption of the usual Levodopa dose and always in the morning to minimize variability).

The assessments were performed at baseline (T0) and at the end of training period (T1) by trained professionals who were not involved in other study phases (enrollment, randomization or treatment) and who were blinded to group assignment.

The same evaluators administered the UPDRS at T0 and T1 for every participant. The UPDRS was scored by clinicians specialized in movement disorders and trained for its administration and interpretation. All raters involved in the study underwent a preliminary course to harmonize methods and increase inter-rater reliability to a Cronbach alpha −0.8.

2.6. Post-hoc analysis

To determine whether walking disability or FOG could differentially affect individual responsiveness to each type of gait training, participants were classified as dependent or independent walkers according to their ability to walk with assistance (UPDRS I item 15 = 3) or without assistance (UPDRS II item 15 = 1–2). Moreover, they were classified as freezers and non-freezers based on the presence of FOG (UPDRS II item 14 $\geq$ 1) or absence of FOG (UPDRS II item 14 = 0).

3. Sample size calculation

Sample size calculation was based on the findings of previous controlled trials with similar intervention protocols for both RAGT and TT involving pwPD [3,19]. Considering that 6MWT well reflects global disease-related walking disability in pwPD [21] and assuming that the response within each group is normally distributed with SD 30 and the expected true difference in the experimental and control means is $\geq$ 20, we needed to include 48 individuals in each group (RAGT and TT) to reject the null hypothesis that the population means of the experimental and control groups were equal with statistical power 0.90 and probability 0.05.

4. Statistical analysis

The normal distribution of continuous variables (age, disease duration, UPDRS, TUG, 10MWT, 6MWT, PDQ-39) was checked considering skewness, excess kurtosis of baseline scores and z-tests for both skewness and kurtosis. In addition, visual assessment of the Q-Q plot was used to confirm normality. Thus, data for all normally distributed variables are described with mean (SD) and were analyzed by Anova for repeated measures (Anova-RM) and Fisher test for post-hoc comparison. Otherwise, they were treated as non-parametric variables and described with median (range) and Q1–Q3 and were analyzed by non-parametric data tools: Wilcoxon test to detect within-group changes after treatment and Mann-Whitney U test for between-group comparisons. Clinical changes associated with the therapy were assessed by "T1-T0" absolute differences and compared between groups: the effect size was calculated by using Cohen's *d*. We also report results as percentage improvement at T1 vs. T0. When available, the Minimal Clinically Important Difference (MCID) was considered to test the clinical relevance of absolute changes. Categorical variables are described with number (%) and were compared by Chi^2 test. The probability to achieve a MCID was calculated for both groups, estimating odds ratios (ORs) as a measure of the effect size with 95% confidence intervals. The inter-center and inter-group homogeneity at T0 was verified. Statistical significance was set at $P < 0.05$. SAS Stat View 5.0 was used for statistical analysis.

This study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee (no. 12/2014 of December 3, 2014). Participants were included in the study after signing an informed consent according to Italian law.

Trial registration: ClinicalTrials.gov (NCT01668407).

5. Results

Among the 161 screened participants, 110 were eligible for the study and were allocated to RAGT ($n = 60$) or TT ($n = 50$). Eight participants dropped out within the first 10 days of enrolment and before starting treatment because of drug changes or medical complications, and 6 discontinued the treatment after 2 to 3 sessions. Eventually, 96 participants, 48 per group, completed the study (Fig. 1). The mean (SD) age was 67.6 (8.7) years and mean disease duration 8.9 (4.8) years (Table 2). The proportion of participants with Hoehn and Yahr stage 2–4 in the OFF condition was 36.5% for stage 2, 11.5% stage 2.5, 38.5% stage 3 and 13.5% stage 4. All participants received chronic anti-parkinsonian drugs including levodopa (89%) dopamine-agonists (65%) or an inhibitor of monoamine oxidase B (66%). At T0, the 2 groups did not differ in demographic features (age, sex) or clinical data (disease duration, levodopa equivalent daily dose, Hoehn and Yahr stage, MMSE score, prevalence of dependent walkers or freezers) (Table 2). Primary and secondary outcome measures were also equally distributed.

Both RAGT and TT groups showed improvement in all outcome measures after treatment. Results of the descriptive and comparative statistics are in Table 3.

5.1. Primary outcomes

6MWT increased by about 35 m, that is, 18%, as compared with T1; 48% participants in the TT group showed improvement beyond the MCID [28] vs. 21% in the RAGT group, although this difference was only mildly significant, as assessed by the OR reported in Table 4. The TUG test score decreased by 2 s (12%) in the whole sample, 59% of RAGT participants and 76% of TT participants showing improvement beyond the MCID. The 10MWT score decreased by

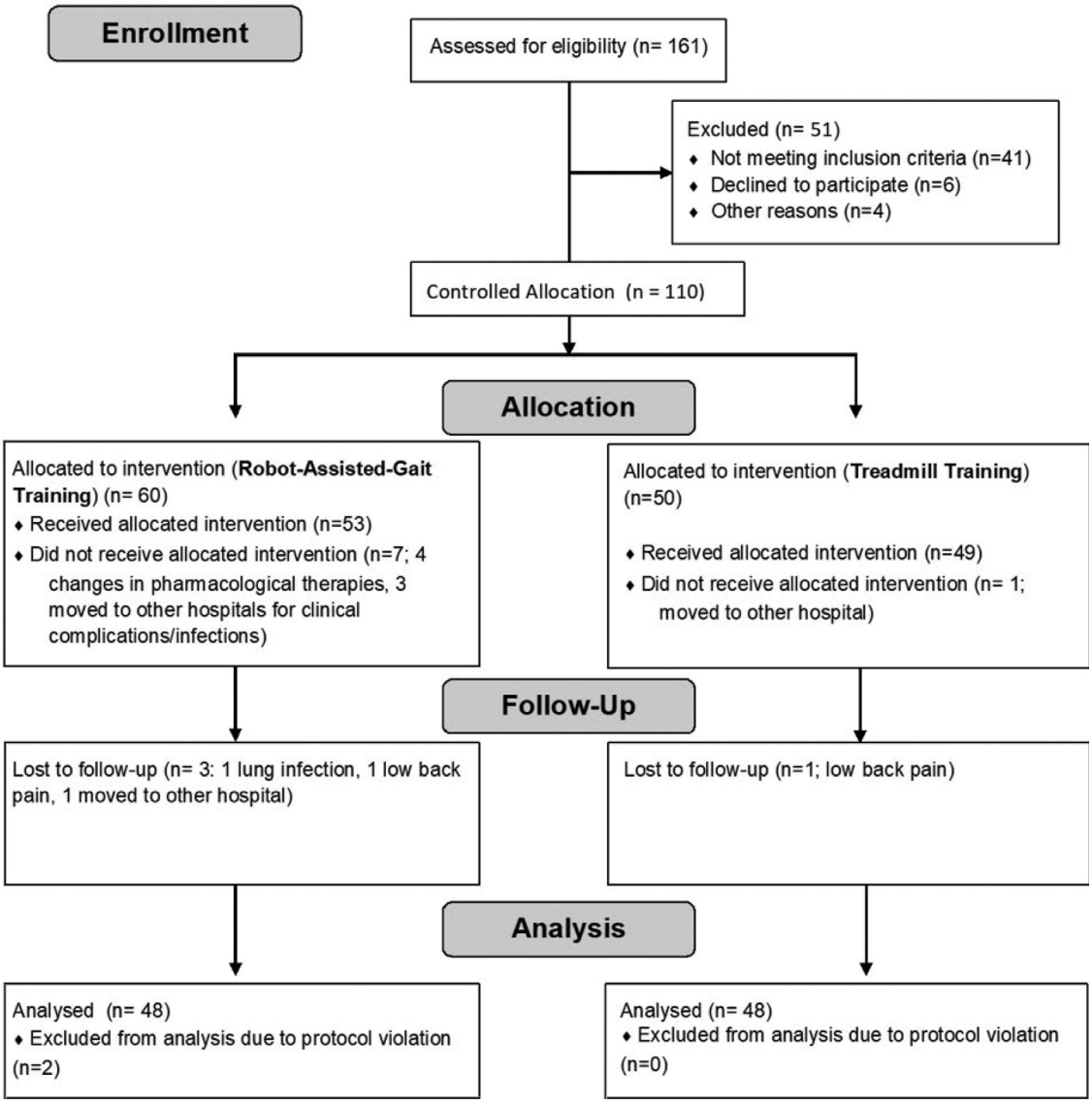

Fig. 1. Flow of participants in the study.

0.1 m/s (16%), about 45% of participants in both groups showing improvement beyond the MCID (Table 4).

5.2. Secondary outcomes

The FOG-Q score improved after either treatment, decreasing by about 3.1 points in with RAGT and 1.5 points with TT (Table 3), with a significant time × treatment effect in favour of RAGT ($F = 4.6$; $P = 0.03$) and medium effect size (Cohen's d: 0.50).

The WHS score was improved in all participants, with no treatment-related differences.

The UPDRS total score, UPDRS II and III subtotal scores and PDQ-39 score decreased by 17%, 16%, 12% and 15%, respectively, in the whole sample. The UPDRS total score showed a significant time × treatment effect in favour of RAGT, 46% of participants showing improvement beyond MCID as compared with 17% in the TT group ($Chi^2 = 8.3$, $P = 0.003$) (Table 4).

5.3. Post-hoc analysis

FOG was present in 63/96 (66%) participants. At T0, freezers differed from non-freezers in longer mean (SD) disease duration (9. [5.2] vs. 6. [3]; $t = -5.9$, $P < 0.0001$), higher mean UPDRS total score (4 [24] vs. 38 [14]; $t = 2.2$, $P = 0.03$) and lower mean MMSE score (26 [1.8] vs. 28 [1.5]; $t = 2.8$, $P = 0.006$). Moreover, FOG was reported significantly more by dependent walkers (99% freezers) than independent walkers (52% freezers). Overall, 40 (63%) freezers presented OFF-FOG, 19 (30%) resistant-FOG and 4 (6%) ON FOG. This distribution was similar in both groups.

Post-hoc analysis highlighted mitigated disease-related disability (UPDRS II score) more in freezers than non-freezers, regardless of treatment group ($F = 5.5$; $P = 0.02$).

In freezers, the FOG-Q score was improved by a mean of 4.5 points after RAGT ($t = 5.3$; $P < 0.0001$) and 2.1 after TT ($t = 5.6$; $P < 0.0001$); the subgroup (freezers vs. non-freezers) × treatment effect was statistically significant ($F = 4.2$; $P = 0.04$; Cohen's $d = 0.61$) (Fig. 2A).

Congruently, dependent walkers in the RAGT group showed greater change in FOG-Q score (mean difference 3.3; $t = 3.4$; $P = 0.003$) than dependent walkers in the TT group (mean difference 2.8; $t = 5.7$; $P < 0.0001$) as did independent walkers in the RAGT group (mean difference 2.8; $t = 3.2$; $P = 0.003$) and independent walkers in the TT group (mean difference 1.1; $t = 2.8$; $P = 0.01$) (Fig. 2B). No other inter-group differences were found in the post-hoc analysis.

Table 2
Demographic and clinical profile of the 2 treatment groups, RAGT and treadmill training (TT), at baseline.

	Total sample $n=96$	RAGT $n=48$	TT $n=48$	Between-group comparison
Age (years), mean (SD)	67.6 (8.7)	68.1 (9.8)	67.0 (7.6)	F = 0.4; *P* = 0.5
Female, n *(%)*	53 (55)	29 (60)	24 (50)	Chi^2 = 1.0; *P* = 0.3
Disease duration (years), mean (SD)	8.9 (4.8)	8.9 (5.3)	8.9 (4.3)	F = 4.4^{-4}; *P* = 0.98
Age at the onset (years), mean (SD)	58.7 (9.9)	59.2 (10.8)	58.1 (8.9)	F = 0.4; *P* = 0.5
Hoehn and Yahr, median [range]; Q1–Q3	3 [2–4]; 1.0	3 [2–4]; 1	3 [2–4]; 1.0	Chi^2 = 0.4; *P* = 0.8
LEDD (mg), mean (SD)	739.6 (310)	739.8 (328)	739.4 (301)	F = 4.3^{-5}; *P* = 0.99
DA-LEDD (mg), mean (SD)	111.3 (102)	105.3 (112)	115.3 (96)	F = 3.2^{-2}; *P* = 0.95
MMSE, mean (SD)	26.5 (2.1)	26.1 (2.0)	26.8 (2.1)	F = 1.8; *P* = 0.2
UPDRS part II item 14, median [range]; Q1–Q3	2 [1–3]; 2	2 [1–3]; 1.5	2 [1–3]; 2	Chi^2 = 0.3; *P* = 0.8
Non-freezers: score 0, *n* (%)	33 (34)	16 (32)	17 (37)	Chi^2 = 0.3; *P* = 0.5
Freezers: score 1–3, *n* (%)	63 (66)	32 (68)	31 (63)	Chi^2 = 0.4; *P* = 0.8
UPDRS part II item 15, median [range]; Q1–Q3	2 [1–3]; 2	2 [1–3]; 2	2 [1–3]; 2	Chi^2 = 1.2; *P* = 0.7
Independent walkers: score 1–2, *n* (%)	63 (65)	28 (58)	35 (73)	Chi^2 = 2.5; *P* = 0.1
Dependent walkers: score 3, *n* (%)	33 (35)	20 (42)	13 (27)	Chi^2 = 2.6; *P* = 0.1

LEDD: levodopa equivalent daily dose; DA-LEDD: dopamine-agonists-LEDD; MMSE: Mini Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; UPDRS part II item 14 = freezing; UPDRS part II item 15 = walking.

Table 3
Pre-post treatment changes in primary and secondary endpoints in the 2 treatment groups, RAGT and TT.

Outcome measures	Group	T0	T1	% change T1-T0 *n* (%)	Change T1-T0	Time effect	Time × treatment effect	Effect size (Cohen's *d*)[a] (95% CI)
6MWT (m)	**RAGT**	280.7 (95.8)	298.8 (122.2)	9.1 (38)	18.2 (87)	**F = 18.7 *P* < 0.0001**	F = 0.27; *P* = 0.6	0.40 (0.00–0.8)
	TT	278.5 (116)	325.3 (103.3)	24 (25)	46.8 (48.4)			
TUG (s)	**RAGT**	17.8 (9.)8	16.3 (11.4)	−10 (19)	1.4 (5.2)	**F = 18.8 *P* < 0.0001**	F = 2.6; *P* = 0.11	0.35 (−0.7 to 0.05)
	TT	20.0 (11.0)	16.8 (8.6)	−14 (14)	3.1 (4.4)			
10MWT (m/s)	**RAGT**	0.9 (0.3)	1.0 (0.3)	11 (30)	0.10 (0.2)	**F = 28.1 *P* < 0.0001**	F = 1.8; *P* = 0.18	0.25 (−0.7 to 0.05)
	TT	0.9 (0.3)	1.0 (0.3)	23 (32)	0.15 (0.2)			
FOG-Q	**RAGT**	9.9 (7.0)	6.8 (5.9)	−28 (41)	3.1 (4.4)	**F = 42.5 *P* < 0.0001**	**F = 4.6; *P* = 0.03**	**0.50 (0.05–0.86)**
	TT	8.9 (6.1)	7.3 (5.6)	−18 (39)	1.5 (2.1)			
UPDRS II Item 14: freezing	**RAGT**	1.4 (0.9)	0.7 (0.8)		−0.69 (0.81)	**F = 45.5 *P* < 0.0001**	**F = 8.9; *P* = 0.004**	**0.61 (0.2–1.02)**
	TT	1.4 (0.1)	1.1 (0.9)		−0.27 (0.54)			
WHS	**RAGT**	3.8 (1.3)	4.0 (1.3)	9 (19)	0.25 (0.5)	**F = 13.1 *P* = 0.0005**	F = 1.4; *P* = 0.23	0.26 (−0.1 to 0.66)
	TT	4.2 (1.2)	4.3 (1.2)	5 (16)	0.12 (0.5)			
UPDRS TOT	**RAGT**	46.9 (22.5)	33.4 (17.0)	−26 (22)	13.6 (16.1)	**F = 63.3 *P* < 0.0001**	**F = 5.8; *P* = 0.02**	**0.51 (0.1≠0.9)**
	TT	47.6 (26.5)	40.4 (21.0)	−14 (11)	7.2 (7.7)			
UPDRS II	**RAGT**	13.5 (6.0)	10.8 (5.7)	−20 (21)	2.6 (3)	**F = 70.0 *P* < 0.0001**	F = 2.1; *P* = 0.15	0.29 (−0.1 to 0.7)
	TT	15.5 (7.1)	13.67 (6.1)	−11 (14)	1.8 (2.2)			
UPDRS III	**RAGT**	22.4 (9.5)	19.5 (8.2)	−12 (14)	2.8 (4.2)	**F = 34.7 *P* < 0.0001**	F = 0.4; *P* = 0.5	0.20 (−0.56 to 0.23)
	TT	24.9 (16.7)	21.3 (12.9)	−11 (18)	3.6 (5.6)			
PDQ-39	**RAGT**	55.9 (30.8)	49.7 (29.7)	−16 (23)	6.2 (12.1)	**F = 41.9 *P* < 0.0001**	F = 1.6; *P* = 0.2	0.29 (−0.69 to 0.11)
	TT	48.5 (28.9)	39.2 (22.47)	−18 (17)	9.3 (8.9)			

Data are mean (SD) unless indicated. The statistical significant results were highlighted with bold characters. FOG-Q: Freezing Of Gait Questionnaire; 10MWT: 10-m Walk Test; 6MWT: 6-min Walk Test; PDQ-39: Parkinson's Disease Quality of life scale-39; TUG: Timed Up and Go test; UPDRS: Unified Parkinson's Disease Rating Scale (TOT = total score; II = part II: ADL score; III = part III: motor score); WHS: Walking Handicap Scale.

[a] The standardized difference between T1-T0 changes in the two groups was computed to provide the effect size (Cohen's *d*). Effect sizes > 0.50 are highlighted as clinically relevant.

6. Discussion

This study, including a large sample of individuals with moderate to advanced PD, confirms that intensive gait training assisted by any electromechanical device, a G-EO system or a treadmill, effectively improved endurance (6MWT), gait capacity (TUG test, 10MWT), performance (FOG-Q, WHS), global independence in activities of daily living (UPDRS part II) and perception of well-being (PDQ-39). RAGT was more effective than TT in reducing FOG-Q score, especially in individuals with greater walking disability.

In the present study, endurance (6MWT) was improved in both groups, although slightly more in TT, whereas gait capacity (10MWT, TUG) improved equally. These findings agree with those from Picelli et al. [13,17,29] and Sale et al. [3] RAGT sets the stride length while varying body weight. Conversely, TT keeps the body weight constant while progressively increasing gait velocity. Both approaches meet the requirements of a progressive exercise, personalizing task difficulties as long as individuals increase their fitness. Likely, the lack of BWS on a treadmill increases the training effort, providing slightly better, although not significant, results in terms of gait endurance [18].

TT is a well-known and widely tested approach for gait rehabilitation in pwPD. It is usually well accepted and tolerated by individuals, never increasing the risk of protocol violations due to dropouts [5–9]. It is also affordable for most rehabilitation facilities.

The superior efficacy of TT over conventional therapy was shown in numerous studies [5] in that TT improved hypokinesia by increasing gait speed and stride length but not gait cadence. Recently, TT was shown to inhibit the pro-oxidative pro-inflammatory state that increases dopaminergic neuron vulnerability and the risk of developing PD with aging [30]. TT is considered a "forced-use therapy" because individuals are driven to produce gait cycles at greater speed than the speed they would automatically select during over-ground walking [31]. Individuals

Table 4
Individuals achieving the Minimal Clinically Important Difference (MCID) in clinical outcomes after treatment.

Outcome measure	MCID	Treatment group	Individuals achieving the MCID *n* (%)	*P* (Chi^2) and effect size OR (95% CI)
6MWT (m)	**34 m** [38]	**RAGT**	12 (21)	Chi^2 = 3.6, *P* = 0.06; 0.24 (0.1–0.6)
		TT	28 (48)	
TUG (s)	**0.8 s** [39]	**RAGT**	22 (59)	Chi^2 = 1.8, *P* = 0.17; 0.25 (0.1–0.6)
		TT	37 (77)	
10MWT (m/s)	**0.14 m/s** [40]	**RAGT**	20 (47)	Chi^2 = .2, *P* = 0.6; 0.99 (0.4–2.2)
		TT	20 (42)	
FOG-Q	**N.E.**	**RAGT**	n.a.	n.a.
		TT		
WHS	**N.E.**	**RAGT**	n.a.	n.a.
		TT		
UPDRS TOT	**4.1 points** [26]	**RAGT**	18 (46)	**Chi^2 = 8.3, *P* = 0.003; 2.94 (1.1–8.1)**
		TT	8 (17)	
UPDRS II	**1.5 points** [26]	**RAGT**	24 (52)	Chi^2 = 2.0, *P* = 0.15; 0.99 (0.4–2.4)
		TT	18 (38)	
UPDRS III	**2.3 points** [26]	**RAGT**	9 (26)	Chi^2.4, *P* = 0.5; 0.56 (0.2–1.4)
		TT	14 (29)	
PDQ-39	**1.6 points** [27]	**RAGT**	15 (33)	Chi^2 = 1.9, *P* = 0.15; 0.76 (0.3–1.8)
		TT	18 (49)	

OR: odds ratio; 95% CI: 95% confidence interval; 10MWT: 100-m Walk Test; 6MWT: 6-min Walk Test; FOG-Q: Freezing Of Gait Questionnaire; N.E.: not established; n.a.: not applicable; PDQ-39: Parkinson's Disease Quality of life scale-39; TUG: Timed Up and Go test; UPDRS: Unified Parkinson's Disease Rating Scale (TOT = total score; II = part II: ADL score; III = part III: motor score); WHS: Walking Handicap Scale; Chi^2: chi-square test.

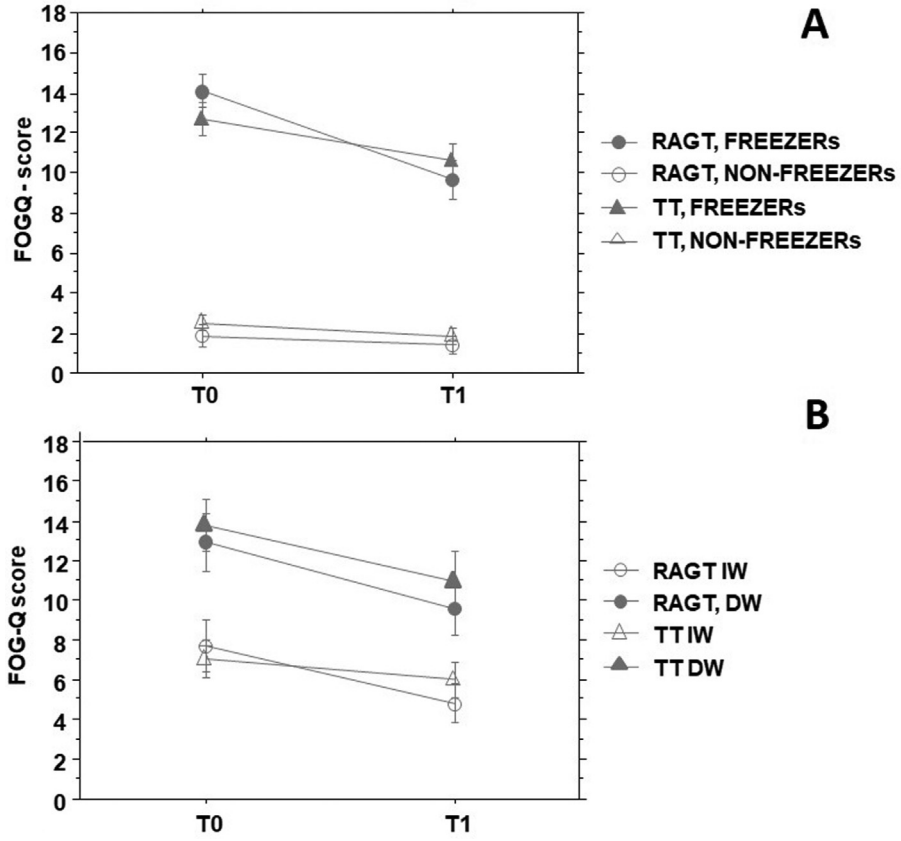

Fig. 2. Change in Freezing of Gait Questionnaire (FOG-Q) score with robot-assisted gait training (RAGT) and treadmill training (TT). DW, dependent walkers; IW, independent walkers.

are able to select their own stride length and cadence during TT according to their hip flexor strength and/or central-driven gait system activity, leading to stride-to-stride variability and stride asymmetry [28].

Robotic devices deliver forced gait training and allow for increasing exercise intensity by at least 4 times with respect to TT [28]. The end-effector system used in this study determines stride length and symmetry, gait cadence and velocity, thus preventing stride variability, providing correct somatosensory feedback during gait from leg extremities, while the hip and pelvis are forced to relearn movements [16]. PwPD at any stage of the disease present variable differences between their usual gait and forced RAGT. This condition may lead the sensorimotor system to detect errors during RAGT, thus possibly enhancing

individuals' capacity to learn from the locomotor task [32] more than during TT.

A few controlled trials have investigated the effect of RAGT (delivered by exoskeleton or end-effector systems) on gait in pwPD, applying both clinical measures (UPDRS, 6MWT, 10MWT, TUG, Berg Balance scale, ABC scale) [3,17] and gait analysis (GAITrite or stereo-photogrammetric systems) [16,20,29]. Several authors reported the superiority of RAGT as compared with over-ground training for gait improvement in the short [15,29] and medium term [17] When RAGT was compared with TT, greater efficacy was demonstrated by instrumental, although not clinical, measures of gait [3,16,19].

Despite few controlled studies (Table 1), a few case series reported the effect of exoskeletons and end-effectors on FOG in pwPD [8–12]. Barbe et al. [11] and Pilleri et al. [12] described the gain in FOG-Q score achieved with Lokomat (Lokomat®-Hocoma, Swizerland) and Gait Trainer GT (Reha-Stim Medtec, Swizerland), respectively. Hence, the advantage provided by robots seems independent of the device and is a treatment-specific effect of RAGT on FOG, occurring regardless of the severity of gait disability. Actually, dependent walkers and freezers seemed to benefit more from RAGT than do less disabled pwPD.

The greater effect of RAGT in freezers and dependent walkers might be due to the sustained and constrained nature of the training. These characteristics may be effective in individuals with greater motor and cognitive impairment. Because individuals with FOG show worse UPDRS III and MMSE scores than those without FOG, they can benefit from a RAGT that forces them to exercise longer and more effectively than they could do over-ground. In fact, in a more ecological scenario, individuals with FOG would never provide a rhythmic stepping at relatively high speed to meet the requirements of intensive training. RAGT also induced a significant gain in the UPDRS total score, mainly attributable to improvement of the UPDRS activities of daily living (ADL) section with a minor contribution of changes in UPDRS I and III scores. Owing to its construction, the UPDRS-ADL is more responsive than the UPDRS III to the improvement of axial symptoms [26].

The perception of well-being improved after either training by about 17%, thus confirming the good acceptance of the electromechanical devices and quality of life dependence on motor symptoms in pwPD [33].

We also assessed a measure of gait performance (WHS) to provide a comprehensive description of participants' function according to the bio-psycho-social model of illness that has been proposed by the World Health Organization in the International Classification of Functioning, Disability and Health (WHO-ICF) [34]. WHS describes walking performance from walking in the community without any restriction to in-door walking only for exercise [25]. The energy cost of walking is the only independent prognostic factor of walking performance as measured by the WHS [34]. In our study, the WHS score improved after treatment in the whole sample.

6.1. Study limitations

The lack of medium- and long-term follow-up is a limitation of the study, challenging the demonstration of exercise impact on motor learning retention. One of the main findings concerns the superior impact of RAGT on FOG-related disability. However, this result is based on a patient-related outcome, the FOG-Q, which can be considered a soft measure [35]. However, the FOG-Q is the only validated test for the diagnosis of freezing, in the absence of any other hard measure at present. The Italian version was provided by Tambasco et al. [24]. The FOG-Q measures a single dimension, has high test-retest reliability and internal reliability and a high correlation with items of the UPDRS relating to walking, general motor issues and mobility. Moreover, FOG-Q item 3 is as reliable as the UPDRS item 14 and more sensitive for screening freezers, [26] and in a longitudinal study, the FOG-Q was a predictor of FOG onset [36]. Conversely, laboratory gait analysis does not add meaningful information on the daily occurrence of FOG and cannot be considered a gold standard for studying this phenomenon [22]. A more ecological gait analysis, possibly delivered at home using wearable systems, could provide objective and reliable data on freezing in pwPD [37].

The block approach to treatment allocation was efficacious to create intervention groups that were similar at baseline for the main confounding factors. Therefore, although the study cohort was not primarily selected, on the basis of FOG presence, the descriptive analysis excluded an unequal distribution of freezers in the 2 treatment groups, thus reducing the possibility of a biased interpretation of findings.

7. Conclusions

For pwPD, electromechanical-assisted gait training, delivered via a treadmill or an end-effector system, led to a significant increase in walking capacity in terms of endurance, speed, and reduction in FOG and also mitigated disability and enhanced the perception of well-being. The benefit seemed to be greater in dependent walkers and freezers, regardless of the device used for gait training, specifically for global disease-related disability. Besides, freezers showed greater advantages from RAGT than TT when considering daily FOG occurrence. Further clinical and neurophysiological studies, using objective home-based gait monitoring and assessing functional changes in the long-term, are warranted to confirm these data and better understand the main factors of training efficacy for pwPD.

Contribution of authors

MC, MGC and MF equally contributed to the conception and design of the work; PS, MC, SP, DG, DLP, MFDP, MP and EA contributed to data collection; MC, PS, MG, MGC and MF contributed to data analysis and interpretation; MC, SP, EA and MGC prepared the draft article, which was critically revised by MF and finally approved by all the authors.

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Disclosure of interest

The authors declare that they have no competing interest.

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