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ARTICLE

Effects of progressive resistance training in individuals with type 2 diabetic polyneuropathy: a randomised assessor-blinded controlled trial

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Abstract

Aims/hypothesis The aim of this study was to evaluate the effects of progressive resistance training (PRT) on muscle strength, intraepidermal nerve fibre density (IENFD) and motor function in individuals with type 2 diabetic polyneuropathy (DPN) and to compare potential adaptations to those of individuals with type 2 diabetes without DPN and healthy controls.

Methods This was an assessor-blinded trial conducted at the Neurology department, Aarhus University Hospital. Adults with type 2 diabetes, with and without DPN and healthy control participants were randomised to either supervised PRT or non-PRT for 12 weeks. Allocation was concealed by a central office unrelated to the study. The co-primary outcomes were muscle strength in terms of the peak torque of the knee and ankle extensors and flexors, and IENFD. Secondary outcome measures included the 6 min walk test (6MWT), five-time sit-to-stand test (FTSST) and postural stability index obtained by static posturography.

Results A total of 109 individuals were enrolled in three groups (type 2 diabetes with DPN [$n = 42$], type 2 diabetes without DPN [$n = 32$] and healthy control [$n = 35$]). PRT resulted in muscle strength gains of the knee extensors and flexors in all three groups using comparative analysis (DPN group, PRT 10.3 ± 9.6 Nm vs non-PRT −0.4 ± 8.2 Nm; non-DPN group, PRT 7.5 ± 5.8 Nm vs non-PRT 0.6 ± 8.8 Nm; healthy control group, PRT 6.3 ± 9.0 Nm vs non-PRT −0.4 ± 8.4 Nm; $p<0.05$, respectively). Following PRT the DPN group improved the 6MWT (PRT 34.6 ± 40.9 m vs non-PRT 2.7 ± 19.6 m; $p=0.001$) and the FTSST (PRT −1.5 ± 2.2 s vs non-PRT 1.5 ± 4.6 s; $p=0.02$). There was no change in IENFD following PRT in any of the groups.

Conclusions/interpretation PRT improved muscle strength of the knee extensors and flexors and motor function in individuals with type 2 diabetic polyneuropathy at levels comparable with those seen in individuals with diabetes without DPN and healthy control individuals, while no effects were observed in IENFD.

Trial registration ClinicalTrials.gov NCT03252132

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Research in context

What is already known about this subject?

- The role of physical exercise as a therapeutic approach in diabetic polyneuropathy (DPN) has emerged from a few recent trials

What is the key question?

- Can progressive resistance training (PRT) lead to improvements in lower-body muscle strength, measures of small fibre structure, motor function, postural stability, symptoms of neuropathy, quality of life and metabolic profile in individuals with type 2 diabetic polyneuropathy?

What are the new findings?

- PRT leads to improved muscle strength and motor function in individuals with type 2 diabetes and DPN at a level comparable with that seen in diabetic individuals without DPN and healthy control individuals; no effect on small nerve fibre structure was observed

How might this impact on clinical practice in the foreseeable future?

- The findings provide evidence for establishing PRT exercise protocols for individuals with type 2 diabetes and DPN as PRT contributes to the non-pharmacological treatment options recommended for individuals with DPN

Keywords Diabetic polyneuropathy · Exercise · Motor function · Muscle strength · Progressive resistance training · Small nerve fibre structure

Abbreviations

DPN	Diabetic polyneuropathy
FTSST	Five-time sit-to-stand test
IENFD	Intraepidermal nerve fibre density
NCS	Nerve conduction studies
1RM	One-repetition maximum
PRT	Progressive resistance training
QoL	Quality of life
6MWT	6 min walk test
ST	Stability index
TCNS	Toronto Clinical Neuropathy Score

Introduction

Distal symmetric diabetic polyneuropathy (DPN) is the most common chronic complication in individuals with type 2 diabetes, affecting up to 50% [1]. DPN leads to decreased sensation in the feet, poor balance, altered gait and motor dysfunction [2]. These physical disabilities may result in a sedentary lifestyle, further contributing to the progression of diabetes-related complications.

Currently, there are no curative therapies for individuals with DPN. Treatment and prevention guidelines thus focus on lifestyle strategies and pharmacological therapies concerning optimal glycaemic control or pain management [1].

Until recently, DPN was believed to cause irreversible changes. However, a few studies have suggested that physical exercise may have beneficial effects on neuropathic symptoms, gait function [3, 4] and epidermal nerve fibre branching [5]. In addition, physical exercise has been shown to prevent or delay diabetes progression [6]. Previously, exercise in individuals with DPN was discouraged due to concerns regarding foot ulcers and other complications related to neuropathy such as amputations. However, studies have documented that exercise in DPN is safe [7], and the role of physical exercise as a therapeutic approach in DPN is emerging from a few recent trials [8].

Most studies of DPN and physical exercise have been conducted in mixed populations of individuals with type 1 diabetes and type 2 diabetes [8–10] and have had limited sample sizes [5, 11, 12] or non-controlled study designs [5], or have used non-validated outcomes and unclear definitions of DPN [10, 12, 13]. Furthermore, most studies have focused on mixed interventions including both aerobic and strength training and/or low-intensity exercises [5, 10, 14, 15] or the sole focus has been on balance and gait training [3, 16–18]. Studies evaluating resistance training per se or in combination with aerobic training have used low-intensity exercises with insufficient loads and progression [12], have had a low exercise frequency [9], or interventions have consisted of only a few training sessions [14]. Consequently, the effect of progressive resistance training (PRT) and its ability to induce neural adaptations,

strength gains and muscle hypertrophy in individuals with DPN remains to be investigated.

PRT has been shown to be effective in improving strength and motor function in individuals with type 2 diabetes [19]. However, the effect of PRT has never been studied in individuals with type 2 diabetes and DPN as compared with those without DPN and healthy control individuals, in a randomised trial design. Thus, it remains unclear to what extent individuals with type 2 diabetes and DPN will gain muscle strength and improve postural stability, intraepidermal nerve fibre density (IENFD; a measure of small fibre structure) and motor function following PRT.

We hypothesised that in individuals with type 2 diabetes and DPN, PRT can improve lower-body muscle strength, motor function, postural stability and IENFD, and that the strength gains are comparable with those obtained in individuals with type 2 diabetes without DPN and in individuals without diabetes.

The aim of our study was to evaluate the effects of a 12 week PRT intervention on muscle strength of the ankle and knee extensors and flexors, IENFD and motor function in individuals with type 2 diabetes with and without DPN; moreover, to compare these adaptations with those in healthy control individuals.

Methods

Trial design

This study was a 12 week randomised supervised training trial conducted at the Department of Neurology, Aarhus University Hospital, Denmark. Individuals underwent a baseline evaluation including a detailed interview, physical examinations with neuropathy scoring, isokinetic dynamometry, walking performance, mobility and postural stability. Eligible individuals were then randomly assigned to receive training or no training. The study recruitment started in August 2017 and the last follow-up visit was performed in February 2019.

Study population

Adults diagnosed with type 2 diabetes according to the 1999 WHO criteria [20] with and without DPN, and healthy control individuals were enrolled at Aarhus University Hospital. Inclusion criteria for individuals were age between 18 and 80 years and ability to independently manage transportation to the training facilities. Exclusion criteria were any other cause of neuropathy apart from diabetes, and prior stroke, ischaemic heart disease, cancer or any other condition that could limit maximal effort performance during training. Individuals who had performed physical exercise or PRT regularly for more than 1 h per week within the last 3 months were excluded.

Individuals were recruited from the Danish diabetes type 2 cohort (DD2) [21] and Department of Endocrinology and Internal Medicine and Department of Neurology at Aarhus University Hospital in Denmark. All individuals provided written informed consent. The study was approved by the Central Denmark Region Committees on Health Research Ethics (approval no. 1-10-72-282-16) and was registered at ClinicalTrials.gov (registration no. NCT03252132).

DPN assessment

All participants underwent a clinical evaluation at baseline and at follow-up. At baseline, all individuals underwent nerve conduction studies (NCS) to determine whether they had DPN. Individuals were assigned to the DPN group according to the Toronto criteria of confirmed neuropathy [22]. DPN was defined as a symptom and/or a sign of DPN assessed by Toronto Clinical Neuropathy Score (TCNS) and combined with abnormal NCS findings in at least two separate nerves, of which one should be the sural nerve [22].

PRT

PRT is a concept where the external resistance increases periodically to ensure gradual continued strength improvements over time [23]. The intervention consisted of 12 weeks of supervised PRT. All training sessions took place at Exercise Biology, Department of Public Health, Aarhus University, Denmark. Each training session lasted approximately 1 h and was supervised by two trained instructors. The exercises consisted of upper- and lower-body exercises including leg press, bench press, pull-downs, knee flexion/extension, ankle plantar and dorsal flexion, abdominal crunches and back extensions. During the first visit, a one-repetition maximum (1RM) was assessed for each exercise, as this reflects the near-maximal muscle dynamic strength and allows for calculation of proper weight loading. Training schedules were individualised and submaximal loads were calculated based on the individual 1RM. Every resistance training session was preceded by a warm-up of 10 min on a stationary ergometer bicycle at moderate intensity. The instructors documented the training load for each exercise in a training diary and ensured that all individuals performed the exercises with technical proficiency and adhered to the training regimen shown in electronic supplementary material (ESM) Table 1. To ensure progressive loading throughout the training period, loads were incrementally adjusted to keep the intensity at target level.

Adherence and dropout

The training programme lasted 12 weeks with two or three sessions per week (30 planned sessions in total). Adherence was assessed as the number of attended training sessions relative to the total number of planned sessions. Irrespective of adherence to the training programme, all individuals completing both baseline and follow-up visits were included in the analyses.

Other assessments

At baseline and follow-up, all individuals underwent a physical examination including measurement of height, weight and waist circumference. Systolic and diastolic BP and resting heart rate were measured three times at 5 min intervals. Individuals provided information on smoking habits, alcohol consumption, level of education and weekly exercise. Blood samples were collected and analysed for HbA_{1c}, total cholesterol, HDL-cholesterol, LDL-cholesterol, triacylglycerols, creatine kinase, plasma glucose, serum creatinine and eGFR.

Main outcome measures

Outcome definitions The primary outcome was muscle strength defined as the maximal peak torque measured by isokinetic dynamometry of the non-dominant ankle and knee to ensure a uniform and comparable measurement across all individuals. A co-primary outcome was IENFD as a measure of small fibre structure.

Motor function Muscle strength was the primary outcome determined by the peak torque measured by isokinetic dynamometry (Biodex System 3; Biodex Medical Systems, Shirley, NY, USA). Maximal isokinetic strength was determined for knee flexors/extensors and ankle dorsal/plantar flexors according to standardised protocols (described in detail elsewhere [24]) with eight repetitions. The upper limit for CV was set at 15% for the ankle joint and 12% for the knee. If the CV exceeded this value, individuals repeated the test up to three times. If the CV still exceeded the set limit, data were not included in further analyses. Walking capacity was assessed by a 6 min walk test (6MWT) according to the American Thoracic Society statements [25]. To describe mobility and strength in transitional movement, a five-time sit-to-stand test (FTSST) was applied as described by Møller et al [26].

Measures of small fibre structure The IENFD and growth-associated protein (GAP-43) fibre density were assessed. Skin punch biopsies (3 mm) were obtained during the primary visit before randomisation and again at follow-up, taken from the non-dominant ankle 10 cm proximal to the lateral malleolus. The staining procedure for IENFD was performed according to published guidelines [27–29].

Static balance measurements Postural instability was assessed by a validated [30] balance system (Tetrax, Israel) consisting of four force plates stabilising the forefoot and heel. The test measures the reaction of ground force pressure applied. To obtain a quantified measurement of the centre of pressure movements of the body, the force platform measures the ground reaction forces generated by a body standing or moving across the platform. Stability on the platform was expressed as a stability index (ST) assessed for 32 s in eight different positions [31].

Participant-reported outcomes Participants were asked to fill out six validated questionnaires during the two visits to assess the effects of exercise on their quality of life (QoL) (well-being index, WHO-5 [32]), mental and physical health (SF-12 version 2 [32]), neuropathy symptoms (MNSI-q [33]), neuropathic pain (DN4 [34]), symptoms of depression (major depression scale ICD-10 [32]; http://apps.who.int/classifications/icd10/browse/2016/en), fatigue (fatigue severity scale [FSS] [21]) and fear of falling (falls efficacy scale [FES-I] [35]).

Sample size

Sample size was estimated for the primary outcome of isokinetic muscle strength of the knee joint (combined muscle strength of the knee extensors and knee flexors). The sample size was calculated as the change in muscle strength at the knee joint from baseline after 12 weeks of PRT. Assuming a mean ± SD change in muscle strength at the knee joint in the PRT group of 27 ± 33 Nm, a mean ± SD change in muscle strength at the knee joint in the control group of −7 ± 19 Nm, $\alpha = 0.05$ and a power of 0.80, the required sample size is 12 in each of the two groups (training and non-training) using a two-sample comparison of means (unpaired t test) [36]. Estimating a potential attrition rate, we decided to include 40 individuals in each group. The recruitment was ended when there was 30 individuals in each group to ensure statistical power.

Randomisation, allocation and blinding

In all three groups, eligible individuals were randomised on the day following the baseline examinations to either training or no training and stratified by biological sex. Random allocation was performed as minimisation using the software 'Minim' [37]. All procedures related to the randomisation were performed at a central office by a researcher not involved in examination, testing, data collection or training. An unblinded study nurse ensured that individuals received

adequate information according to the randomisation. The training instructors were blinded to individual randomisation group and the study design. All examinations and outcome measurements were performed by the same blinded examiner. All participants were instructed not to disclose their group to other individuals and at the initial visit and follow-up visit. At the end of the study, the allocation of individuals was double-checked for correct allocation.

Statistical analysis

Statistical analyses were performed using Stata I/C version 14.2 (StataCorp, USA) and the level of significance was set at $p<0.05$. Descriptive statistics were presented as means ± SD and compared across the three main groups (type 2 diabetes with or without DPN and healthy control group) by ANOVA, whereas exercise and non-exercising subgroups (e.g. training vs not training in healthy control group) were not compared at baseline in accordance with the CONSORT statement [38]. Data were tested for normal distribution by reviewing graphical distributions and interpersonal variance was tested by Bland–Altman plots to identify any systematic differences in the measurements or any outliers. Data on the effect of exercise are presented as means ± SD with 95% CIs. Subsequently, comparisons between exercising and non-exercising subgroups were initially done by *t* statistics. Then, ANOVA was used to test the null hypothesis of no difference between the effects of the PRT intervention between groups of healthy control participants and participants with type 2 diabetes with DPN or without DPN. The outcomes were assessed according to a per protocol analysis.

To estimate associations between muscle strength and the 6MWT, Pearson *r* was used. To test for difference in adherence between the training groups, the Kruskal–Wallis one-way ANOVA was applied and data were presented as medians (interquartile interval).

Results

Among the 139 individuals screened, 109 were found eligible and included in the current trial as follows: individuals with type 2 diabetes and DPN (n = 42); individuals with type 2 diabetes without DPN (n = 32); and healthy control individuals (n = 35) (Fig. 1). During the trial period, 19 participants (17%) dropped out and 90 finished the trial (30 in each group). Reasons for dropping out are presented in Fig. 1. Participants completing the trial were distributed as follows: type 2 diabetes with DPN (n = 15 training, n = 15 no training); type 2 diabetes without DPN (n = 13 training, n = 17 no training); and healthy control group (n = 14 training, n = 16 no training).

Baseline comparisons between the three main groups

Characteristics of the participants are presented in Table 1. Individuals included were of White (northern European) descent, except for five individuals of Mediterranean (n = 2), Middle Eastern (n = 1), Southwest Asian (n = 1) and South American (n = 1) descent. At baseline, there were no significant differences in age, biological sex, diabetes duration, renal function, BP, smoking status, alcohol consumption, level of education or level of physical activity between groups. Furthermore, there were no differences in muscle strength, except for ankle plantar strength, which was lower in the DPN group. However, individuals with DPN had a higher BMI, lower values for the 6MWT and higher values for FTSST compared with the other groups ($p<0.01$).

Adherence to PRT in the three PRT groups

Adherence to PRT was high, with an overall attendance of median 29.0 (IQR 27–30) sessions across all training groups (healthy control group 29.0 [27.8–30.0], individuals without DPN 29.0 [27–29], individuals with DPN 29.0 [21–30]) and no significant differences between groups (p=0.87). All training groups gained strength in all exercises as measured by 1RM (ESM Fig. 1).

Effects of PRT on motor function

Participants with diabetes who underwent PRT (vs no PRT) achieved a significant improvement in combined muscle strength at the knee and ankle, regardless of the presence/absence of DPN, whereas no significant difference was seen for the control group (Fig. 2). Analysing the composite knee muscle strength score separately, all three groups showed significant improvements, whereas no improvement was found for ankle muscle strength in any of the groups (Table 2). Due to a too-high CV of maximal isokinetic muscle strength for the ankle plantar flexors, data from two participants were removed from further analysis, including one participant with DPN and one participant without DPN both randomised to the non-training group. Comparing changes in the PRT groups, no differences were found between any of the groups (DPN vs non-DPN vs healthy control group) (Table 2). Changes in secondary outcomes were found following PRT (vs non-PRT) in the 6MWT and FTSST in individuals with DPN only. Including both groups with diabetes (DPN and non-DPN), the change in combined muscle strength was associated with the change in the 6MWT (r = 0.53, p=0.001) and the FTSST (r = 0.34, p=0.001) (ESM Fig. 2a, b).

Effects of PRT on IENFD, neuropathy, balance, questionnaire scores and metabolic profile

Skin biopsy samples were collected from 27 healthy control participants (non-PRT, n = 16; PRT, n = 11), 20 participants without DPN (non-PRT, n = 12; PRT, n = 8) and 24 participants with DPN (non-PRT, n = 12; PRT, n = 12). When comparing the PRT groups with the non-PRT groups, none of the groups showed significant improvements in IENFD or any of the clinical scores of DPN at follow-up (ESM Table 2). None of the groups showed significant changes in postural stability and only healthy control individuals showed improved balance in the neutral head positions. Furthermore, PRT, compared with no PRT, did not result in changes in any of the groups concerning depression, fatigue, fear of falling, neuropathy symptoms (ESM Table 3) or clinical characteristics (Table 2). Healthy control participants in the non-PRT group improved their QoL and mental health and individuals with diabetes without DPN in the PRT group improved their physical health compared with those in the non-PRT group (ESM Table 3). No changes were observed for BMI, lipid or diabetes profiles including HbA_{1c} following PRT in individuals with diabetes (Table 2 and ESM Table 2).

Adverse events

No serious study-related adverse events due to PRT were reported in any of the PRT groups (Fig. 1). One participant developed muscle pain and one developed ankle joint pain. Two participants in the DPN group had an amputation of a

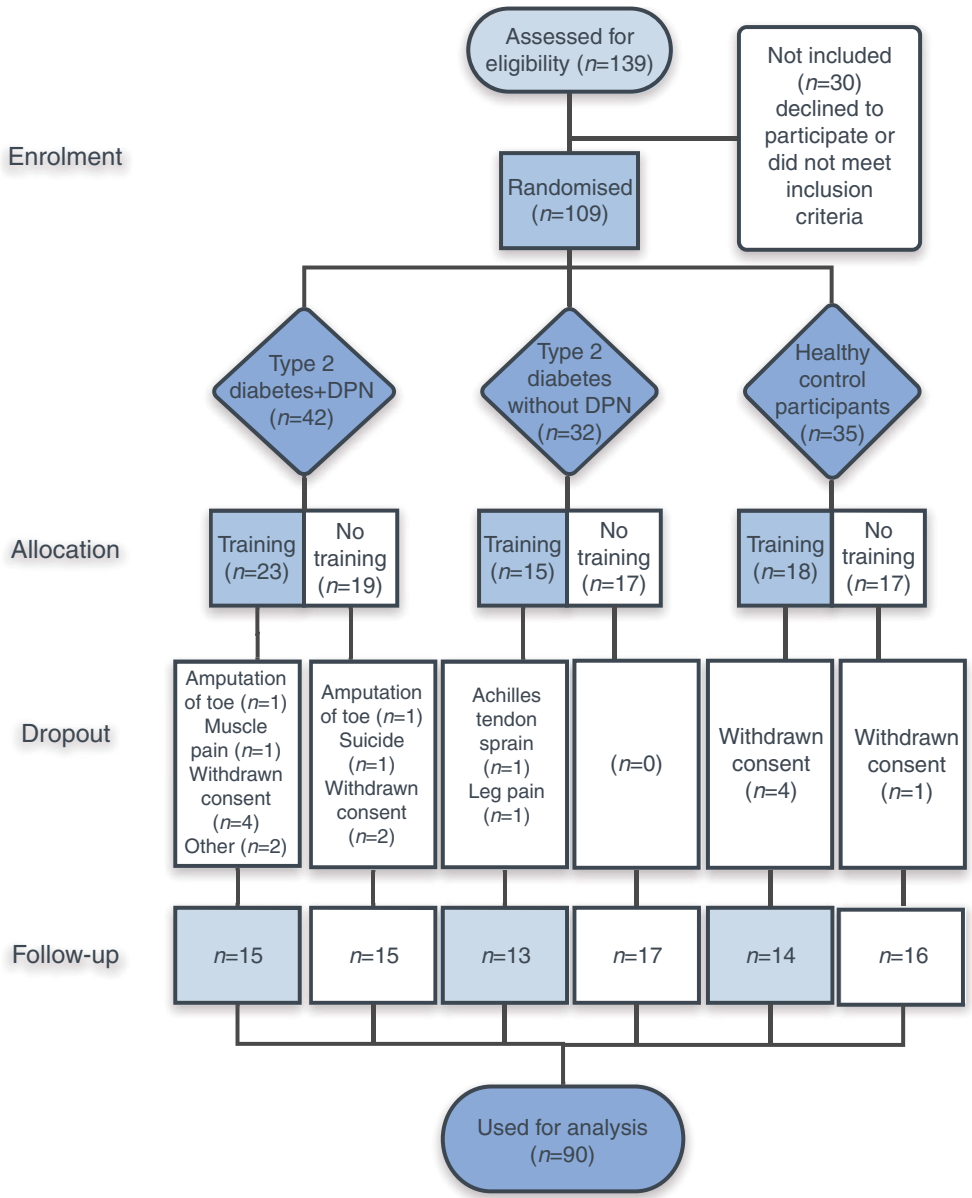

Fig. 1 Flowchart illustrating the study design, enrolment, allocation, dropout and follow-up

Table 1 Baseline characteristics of individuals

Characteristic	Healthy control group (n = 30)	Individuals without DPN (n = 30)	Individuals with DPN (n = 30)	p value
Age, years	62 ± 7	62 ± 9	63 ± 8	0.96
Female sex, n (%)	12 (40)	19 (63)	10 (33)	0.05
Height, cm	176 ± 7	169 ± 7	174 ± 10	0.01
Weight, kg	88 ± 17	91 ± 18	103 ± 19	0.01
BMI (kg/m^2)	29 ± 5	32 ± 6	34 ± 5	0.01
Waist circumference in women, cm	101 ± 23	107 ± 15	113 ± 12	0.27
Waist circumference in men, cm	104 ± 9	115 ± 13	122 ± 13	0.01
Diabetes profile				
Diabetes duration, years	NA	8 ± 5	10 ± 8	0.16
HbA_{1c}, mmol/mol	37 ± 4	52 ± 9	58 ± 14	0.01
HbA_{1c}, %	5.6 ± 0.3	6.9 ± 0.9	7.4 ± 1.2	0.01
Insulin treatment, n (%)	NA	4 (13)	15 (50)	0.01
Oral glucose-lowering agent, n (%)	NA	26 (87)	28 (93)	0.01
BP profile				
Systolic BP (mmHg)	142 ± 21	137 ± 17	140 ± 22	0.37
Diastolic BP (mmHg)	84 ± 12	83 ± 9	85 ± 11	0.66
Antihypertensive medication, n (%)	5 (17)	23 (77)	23 (77)	0.01
Lipid profile				
Total cholesterol, mmol/l	5.4 ± 0.8	4.4 ± 0.8	3.8 ± 1.1	0.01
LDL-cholesterol (mmol/l)	3.1 ± 0.7	2.2 ± 0.8	1.6 ± 0.8	0.01
HDL-cholesterol (mmol/l)	1.6 ± 0.5	1.3 ± 0.4	1.2 ± 0.4	0.01
Triacylglycerols (mmol/l)	1.6 ± 0.7	2.0 ± 0.9	2.3 ± 1.1	0.01
Lipid-lowering agent, n (%)	2 (7)	25 (83)	24 (80)	0.01
Kidney and muscle panel				
Serum creatinine, μmol/l	74 ± 10	70 ± 10	78 ± 27	0.16
eGFR, ml min $^{-1}$[1.73 m]$^{-2}$	85 ± 6	84 ± 8	81 ± 14	0.23
Creatine kinase, U/l	160 ± 156	110 ± 65	155 ± 106	0.20
Smoking status, n (%)				
Never	16 (53)	10 (33)	8 (27)	
Previous	13 (43)	17 (57)	17 (57)	
Current smoker	1 (3)	3 (10)	5 (17)	0.17
Units of alcohol per week, n (%)				
<7 units	20 (67)	23 (77)	22 (73)	
7–21 units	9 (30)	6 (20)	7 (23)	
>21 units	1 (3)	1 (3)	1 (3)	0.93
Level of education, n (%)				
High-school or lower level	12 (40)	11 (37)	16 (53)	
College or higher level	18 (60)	19 (63)	14 (47)	0.39
Exercise status				
Amount of exercise per week[a], n (%)				
<1	12 (40)	15 (50)	16 (53)	
1 or 2	12 (40)	10 (33)	12 (40)	
≥3	6 (20)	5 (17)	2 (6.7)	0.58
Time spent exercising per week, min	76 ± 54	93 ± 45	106 ± 72	0.43
Muscle strength, Nm				
Ankle plantar flexion	83 ± 24	70 ± 20	62 ± 18	0.01
Ankle dorsal flexion	28 ± 7	26 ± 9	23 ± 6	0.05
Knee-extension	149 ± 41	132 ± 35	133 ± 36	0.14
Knee flexion	77 ± 21	65 ± 17	70 ± 18	0.05
Motor function				
6MWT, m	659 ± 92	562 ± 97	504 ± 85	0.01
FTSST, s	8 ± 2	9 ± 2	11 ± 4	0.01
Neuropathy score				
TCNS	2 ± 2	5 ± 4	9 ± 3	0.01
DN4-positive, n (%)	0 (0)	3 (10)	10 (33)	0.01

Continuous data are presented as mean ± SD and categorical data are presented as n (%)

[a] Amount of exercise per week was defined as the no. of sessions per week

Statistical significance was set at p<0.05

DN4, Douleur Neuropathique 4 questionnaire.

Table 2 Changes in muscle strength, motor function tests, postural stability and neuropathy score after 12 weeks of either PRT or non-PRT in individuals with type 2 diabetes with or without DPN and healthy individuals

Variable	Healthy control group			Individuals without DPN			Individuals with DPN			Between group effect *p* value[a]
	Non-PRT (*n* = 16)	PRT (*n* = 14)	*p* value	Non-PRT (*n* = 17)	PRT (*n* = 13)	*p* value	Non-PRT (*n* = 15)	PRT (*n* = 15)	*p* value	
Muscle strength										
Ankle dorsal, plantar flexion, Nm	−0.7 ± 9.7 (−5.9, 4.5)	−2.2 ± 4 (−4.6, 0.7)	0.58	1.2 ± 13.1 (−5.5, 8.0)	2.6 ± 4.2 (0.1, 5.2)	0.7	−0.3 ± 6.8 (−4.0, 3.5)	4.8 ± 10.2 (−0.9, 11)	0.12	0.36
Knee-extension, knee flexion, Nm	−0.4 ± 8.4 (−4.5, 4)	6.3 ± 9.0 (1.1, 12)	0.04*	0.6 ± 8.8 (−4.0, 5.0)	7.5 ± 5.8 (4.0, 11)	0.02*	−0.4 ± 8.2 (−5.0, 4.1)	10.3 ± 9.6 (5.0, 15.7)	0.002*	0.56
Motor function										
6MWT, m	−19.6 ± 79.7 (−63.7, 24.5)	−6.14± 44 (−31, 19)	0.58	9.2 ± 38.1 (−10.4, 28.8)	9.4 ± 24.4 (−5.3, 24.2)	0.44	2.7 ± 19.6 (−15, 9)	34.6 ± 40.9 (11.9, 57.2)	0.001*	0.2
FTSST, s	−0.6 ± 0.9 (−1, −0.04)	−0.9 ± 1.2 (−1.7, 0.1)	0.4	−0.7 ± 1.4 (−1.4, 0.1)	−1.5 ± 0.9 (−2.1, −0.9)	0.08	1.5 ± 4.6 (−1.2, 4.2)	−1.5 ± 2.2 (−2.8, −0.3)	0.02*	0.06
Postural instability index										
ST in neutral positions	1.2 ± 2.5 (−0.1, 2.5)	−0.9 ± 2.9 (−2.6, 0.7)	0.03*	−1.0 ± 3.5 (−2.8, 0.8)	−0.5 ± 3.2 (−2.5, 1.5)	0.7	−0.9 ± 4.8 (−3.6, 1.8)	0.7 ± 5.5 (−2.6, 4.2)	0.40	0.2
ST in tilt/turn positions	−0.3 ± 5.3 (−3.1, 2.5)	−0.3 ± 4.2 (−2.8, 2.1)	0.9	1.3 ± 4.5 (−1.2, 3.8)	−2 ± 4.6 (−4.7, 0.8)	0.07	1.0 ± 8.5 (−3.7, 5.7)	−3.6 ± 14.2 (−12, 5)	0.3	0.5
Clinical neuropathy score										
TCNS	−1.3 ± 2.5 (−2.7, 0.0)	0.0 ± 1.4 (−0.9, 0.7)	0.1	1 ± 3 (−1.0, 2.1)	−1.3 ± 3.2 (−3.0, 0.2)	0.05	−0.1 ± 2.7 (−2.0, 1.4)	−1 ± 2.7 (−2.5, 0.5)	0.3	0.05
Diabetes and clinical profile										
BMI, kg/m^2	−0.4 ± 1.0 (−0.7, 0.6)	−0.1 ± 1.1 (−0.1 , 0.6)	0.42	0.2 ± 1.8 (−0.6, 1.0)	0.3 ± 0.5 (0.1, 0.6)	0.77	−0.4 ± 1.0 (−0.9, 0.1)	−0.1 ± 1.1 (−0.6, 0.4)	0.42	0.95
Waist circumference in men, cm	−0.4 ± 2.5 (−2.6, 1.7)	−1.1 ± 2.9 (−3.1, 0.1)	0.6	−1.8 ± 5.2 (−7.3, 3.7)	0.5 ± 1.2 (−1.4, 2.5)	0.4	−0.9 ± 3.2 (−3.2, 1.4)	−1.1 ± 3.6 (−4.5, 0.7)	0.5	0.42
Waist circumference in women, cm	−3.5 ± 4.8 (−8.1, 0.9)	−7.8 ± 6.0 (−17, 1.9)	0.2	−2.1 ± 3.0 (−4.2, 0.1)	−2.9 ± 4.5 (−6.4, 0.6)	0.6	1.6 ± 3.5 (−2.7, 6.0)	2.9 ± 1.6 (0.9, 5.0)	0.5	0.32
HbA_{1c}, mmol/mol	0.5 ± 1.2 (−0.1, 1.1)	−0.1 ± 1.1 (−0.6, 0.5)	0.18	2.5 ± 4.0 (0.5, 4.4)	−0.2 ± 3.5 (−2.2, 1.7)	0.07	−0.9 ± 5.5 (−3.7, 1.9)	−3.0 ± 5.2 (−5.6, −0.4)	0.30	0.55
HbA_{1c}, %	0.1 ± 0.1 (−0.0, 0.1)	−0.1 ± 0.1 (−0.1, 0.1)	0.18	0.2 ± 0.4 (0.0, 0.4)	−0.0 ± 0.3 (−0.2, 0.2)	0.07	−0.1 ± 0.5 (−0.4, 0.2)	−0.3 ± 0.5 (−0.5, −0.1)	0.30	0.55

Change from baseline was calculated as difference = postscores – prescores; values are presented as mean difference ± SD (95% CIs)

[a] *p* value comparing differences between three training groups

*$p<0.05$; *t* statistics were used to describe mean differences in muscle strength (Nm) between training and non-training groups

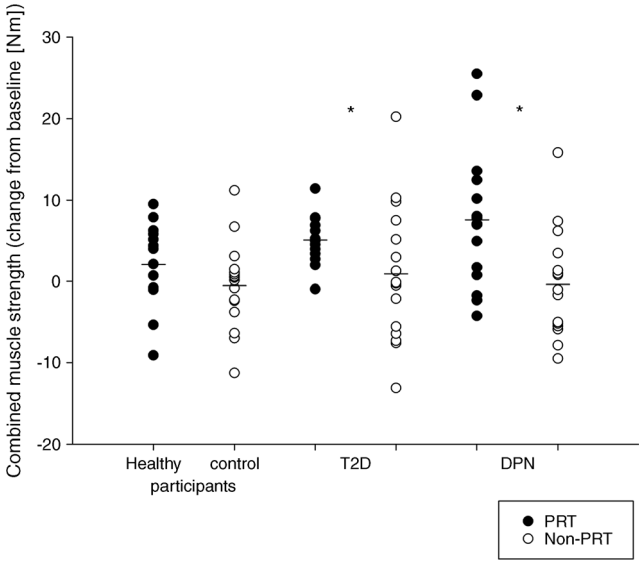

Fig. 2 Change in combined isokinetic muscle strength (change from baseline value in Nm) following 12 weeks of PRT in individuals with type 2 diabetes with DPN (DPN) and without DPN (T2D) and healthy control individuals according to randomisation group (PRT/Non-PRT). The horizontal line represents the mean change in muscle strength within each group. *p<0.05 for PRT vs non-PRT

toe: one in the PRT group; and one in the non-PRT group. None of the participants developed foot ulcers. One individual with DPN randomised to the non-PRT group died by suicide.

Discussion

This study examined the effects of supervised PRT in individuals with type 2 diabetes with and without DPN, compared with healthy controls. Individuals with DPN had a high adherence to the training regimen and showed improved muscle strength, walking distance and speed of transitional movements after PRT compared with individuals with DPN not performing training. The PRT-induced changes were comparable with those seen in both individuals with type 2 diabetes without DPN and in healthy control individuals. Moreover, gains in strength of the knee extensors and flexors were associated with longer walking distance and speed of transitional movements in individuals with diabetes. Our results indicate that PRT should be considered as an add-on treatment option to improve muscle strength and motor function in individuals with DPN.

PRT has been shown to be more effective than low-intensity training in achieving increased muscle strength [39]. It is thus not surprising that most previous studies of individuals with DPN undergoing low-load and low-frequency training interventions have shown insignificant results [12]. Moreover, many studies have solely documented improvements in the trained exercises only (e.g. balance training) [40] without translation into non-specific strength or natural movement patterns reflected by functional tests. Compound resistance exercises targeting the largest muscle groups can increase lean body mass and translate into improvements in natural movement patterns that may affect ambulation [41]. PRT can prevent loss of muscle mass and improve muscle strength, insulin sensitivity, neural control and metabolic markers in individuals with diabetes [41]. However, we did not observe any changes in hyperglycaemic status, BMI, waist circumference or small nerve fibre structure. Individuals trained for 12 weeks, which is sufficient to improve muscle strength and motor function; however, this period might be too short to achieve metabolic improvements. Participants did not receive advice on nutrition, diet and energy intake, which is essential for weight loss.

This is the first study to assess the effects of PRT on measures of small fibre structure in an RCT including participants with and without DPN and healthy control individuals. A few previous studies have suggested IENFD to be a responsive biomarker that may be used in studies examining exercise as a preventive option counteracting neuropathy [42, 43].

Recent studies by Singleton et al [44] and Kluding et al [5] showed that diabetic individuals with and without DPN may show improved IENFD at proximal sites following aerobic and resistance training. However, in a pilot study by Kluding et al [5], DPN was diagnosed at the level of 'probable' only, and Singleton et al [44] examined individuals without neuropathy; thus, these studies might have examined individuals with less-severe nerve injury, with an expectedly larger potential for regeneration. In our study, the participants had confirmed DPN and biopsies were taken from more distal sites as DPN progresses in a distal-to-proximal manner. This could explain the discrepancy between our findings compared with studies examining biopsies taken from more proximal sites. Furthermore, exercise studies by Smith et al [43] and Singleton [44], followed individuals for 12 months; our study, with only 12 weeks of training may have been too short to significantly impact the peripheral nervous system and may explain the lack of improvements on IENFD. As described in our recent review, IENFD does not assess the morphological or molecular characteristics of large fibres [45]. It is therefore possible that changes in large fibres might occur following resistance training. Undergoing a skin biopsy was not mandatory for participating in the study, and 79% of the participants underwent a skin biopsy. Since the sample size in our study was estimated based on muscle strength, the number of participants might have been too small to detect a change in the skin biopsy outcome measures. Finally, no difference was found in clinical neuropathy scales, probably due to their insensitivity to detect subtle changes over shorter time durations [43].

Surprisingly, strength of the ankle plantar and dorsal flexors did not improve in any of the three groups. Other studies have found that distal muscle strength can be improved in individuals with DPN [9]. DPN progresses in a distal-to-

proximal manner and a lack of effect at the ankle may be due to irreversible neurogenic changes in more distal muscle groups [37]. However, this could not be inferred from our study as neither individuals without DPN nor healthy control individuals showed improvement in ankle strength, suggesting that the applied PRT protocol or the assessment of ankle muscle strength may have been suboptimal. It is worth noting that, when using 1RM testing, all participants significantly increased strength of all resistance exercises, both those involving distal and those involving proximal muscle groups (ESM Fig. 2). This discrepancy between 1RM and dynamometry testing could be explained by biomechanical differences between the tests, isolation of muscle groups during dynamometry and the 'learned movement' phenomenon following PRT [46].

Handsaker et al showed that functional tests are highly dependent on muscle strength [9]. Similar improvements in gait endurance have been found during the 6MWT by Mueller et al [12] after weight-bearing exercises, inferring that muscle strength is an important prerequisite for improved mobility and walking. In our study, the gain in muscle strength following PRT was not only statistically significant but also associated with an improvement in the functional tests, 6MWT and FTSST, in all participants with diabetes.

Strengths and limitations

Our study has several limitations. First, participants randomised to the non-PRT group were not advised to refrain from exercising, which could be a confounder, and randomisation to the non-PRT group could have induced observer bias. We did not advise against exercising because we considered this unethical as exercise has numerous beneficial outcomes. However, there were no changes in muscle strength in any of the non-PRT groups indicating that the habitual activity level was maintained during the study period. Second, the study design did not allow for the individuals to be blinded as we did not include sham training. Finally, the trial duration was short and we cannot exclude the possibility that a longer duration of training would have resulted in further improvements.

Study strengths include registration of a detailed medical history for all participants, ensuring exclusion of individuals with other causes of neuropathy and other disorders impeding muscle function. Assignment to the DPN group was based on the findings from both a thorough clinical examination and an extensive evaluation of nerve conduction studies, in contrast to previous studies. To ensure a sufficiently high training intensity, all sessions were supervised and adherence (attended sessions and compliance to the exercise prescription during the sessions) was thoroughly recorded. Isokinetic dynamometry is a validated tool providing 'gold standard' measures of muscle strength on a linear scale; this is in contrast to previous studies using semi-quantitative techniques only.

Our findings provide evidence for establishing PRT exercise protocols for individuals with type 2 diabetes with DPN. Future studies should focus on individuals with more-severe DPN with clinically evident muscle weakness and should include more effective strengthening exercises for the ankle dorsal and plantar flexors. Furthermore, future studies should consider including more proximal biopsy sites and exercise regimens of longer duration.

In summary, PRT led to improvements in muscle strength of the knee extensors and flexors in individuals with DPN, at a level comparable with those seen in individuals with type 2 diabetes without DPN and healthy control individuals. PRT resulted in improvements in motor function, including walking distance and sit-to-stand time.

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Data availability The data used in the analysis reported in this paper will be made available upon request to the corresponding author.

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Contribution statement KSK, HA, KO, UD, TSJ and NBF were responsible for the study design and KSK, HT, LD, SG and PK helped with data collection. KSK, HA, KO, UD and PK were responsible for the statistical analysis and KSK, HA, KO, UD, HT, PK and RPB helped with the interpretation of the data. KSK wrote the first manuscript draft. All authors revised and approved the final manuscript. KSK is the guarantor of this work.

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