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2 Progressive resistance exercise training in Chronic Kidney Disease: A
3 feasibility study.

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Abstract

Patients with chronic kidney disease (CKD) have skeletal muscle wasting, which worsens with progressive decline in renal function and is associated with morbidity and mortality. Resistance exercise is successful at increasing muscle mass in healthy populations, but its use in CKD is under-investigated. Our aim was to determine the feasibility of delivering a supervised progressive resistance exercise programme in patients with CKD with secondary analyses of the effects on muscle size, strength and physical functioning. Patients with CKD stages 3b-4 were randomised to exercise, n=20, or non-exercise controls, n=18. Exercising subjects undertook an eight week progressive resistance exercise leg extension programme at 70% of estimated 1-repetition maximum, three times a week. The non-exercise control group continued with their usual physical activity. Assessments made at baseline and eight weeks were muscle anatomical cross-sectional area (ACSA), angle of pennation and muscle volume by 2D and 3D ultrasonography respectively, isokinetic and isometric knee extensor strength by dynamometry and exercise capacity by shuttle walk test. 33 patients completed the study (87%) and exercising patients attended 92% of training sessions. No changes were seen after eight weeks in the controls for any parameter. Resistance exercise training resulted in significant increases in ACSA ($P=0.006$), muscle volume ($P=0.009$), knee extensor strength ($P=0.001$) and performance in the shuttle walk test ($P=0.01$). Resistance exercise is well tolerated by this patient group and confers important clinical benefits, however low recruitment rates suggest a supervised out-patient based programme is not the most practical implementation strategy.

Introduction

In chronic kidney disease (CKD) skeletal muscle wasting (cachexia) is associated with increased morbidity and mortality.¹ Causative factors include metabolic acidosis, inflammation and oxidative stress, physical inactivity, and peripheral neuropathy, and may be compounded by age related sarcopenia. Skeletal muscle wasting is not limited to those with end-stage renal disease (ESRD), it begins earlier in the course of CKD,² worsening when dialysis is initiated.

Muscle wasting has been associated with both poor tolerance of aerobic exercise, which is known to have cardiovascular benefits in this high risk population³ and an increased risk of all-cause mortality.⁴ Therefore, any intervention which increases muscle mass or prevents this known decline, may impact positively on physical functioning, quality of life, and reduce cardiovascular risk and all-cause mortality. However, exercise and rehabilitation programmes which are widely used in the clinical management of other chronic disease states are not generally available for CKD patients and are under-researched⁵ with little or no data available regarding the practicality and patient acceptability of such an intervention in this population.

Therefore we have investigated the feasibility of an eight week progressive resistance exercise programme in patients with CKD stage 3b-4 with secondary analyses on the effects on muscle size, measured by anatomical cross sectional area (ACSA) and volume, strength and physical functioning. This study aimed to determine patient eligibility numbers, recruitment, retention and adherence rates to give an indication of the acceptability of the exercise intervention for the patients and investigate the effect upon functional outcomes to provide pilot data to inform power calculations for larger trials.

Materials and Methods

Study Design and participants

This was a parallel randomised controlled feasibility study in which 38 subjects with CKD not yet requiring renal replacement therapy (stages 3b-4) were randomly allocated into one of two groups, exercise or control. Subjects randomised to the exercise group were invited to participate in an eight week progressive resistance exercise programme. Assessments of both groups were carried out at baseline and eight weeks. Patients were recruited from nephrology outpatient clinics at the Leicester General Hospital, UK between November 2010 and February 2012 with the intervention period completed in May 2012. Exclusion criteria included; age <40 years, myocardial infarction within the last six months, any unstable chronic condition, physical impairment sufficient to prevent undertaking the resistance protocol, insufficient command of English or inability to give informed consent. Patients with diabetes were not excluded, but HbA1c was required to be <9%. The study design did not include the collection of any information on harms. The study was approved by the National Research Ethics Committee, East Midlands - Leicester ethics committee (Ref 10/H0406/50) and all patients gave written informed consent to participate. A definitive power calculation was not performed because the effect sizes and standard deviations of clinical outcome measures were unknown, and collection of such data was one of the aims of this study. Therefore sample size was pragmatic and resulted from practical recruitment rates. These pilot data can be used to inform power calculations for larger randomised controlled trials.

Randomisation

Patients were randomised to exercise or non-exercising control using the fixed size block method⁶ in block sizes of 10 and group allocation was determined by a series of computer generated random numbers. The randomisation schedule remained hidden from the member of staff performing recruitment and was only revealed after patients had given written informed consent. Due to the nature of the intervention, patients and researchers could not be masked to treatment allocation, but

the researcher performing the ultrasound scans was masked to the baseline values and the researcher quantifying the 3D ultrasound scans was masked to group allocation.

Exercise Intervention

Patients that were randomly allocated to the exercise group were invited to attend exercise training sessions three times a week. Training sessions were preferentially held on non-consecutive days, but at times this was unavoidable. Sessions were under direct supervision of an exercise physiologist on a one-to-one basis. The exercise supervisor recorded the work done in each session. Resistance training consisted of leg extension and leg curl exercises performed on a fixed resistance machine (Powerhouse Fitness, UK) and was preceded and followed by a five minute warm up and cool down on a stationary cycle at approximately 60Watts. Prior to the start of training, subjects performed a ten repetition maximum test and prediction equations were used to estimate one repetition maximum.⁷ The training load in kg, was set at 70% of predicted 1-repetition maximum and subjects performed three sets of 10-12 repetitions of each exercise per session which lasted approximately 30 minutes. When subjects could comfortably complete three sets with good form, the training load was increased. Patients assigned to the non-exercising control group were asked to continue with their usual activity.

Primary Outcome Measures

Recruitment, Retention and Adherence rates

The criterion for success of this pilot study is based upon recruitment, retention and adherence rates. Retention rates were defined as the percentage of patients that completed the study. Adherence rates were defined as the number of completed exercise sessions. For the purposes of this study we defined a successful feasible intervention to have >80% completion rate and >88% attendance at exercise

session. This definition was based upon adherence and drop out rates in other exercise training studies at various stages of CKD disease progression.^{8,9,10}

Secondary Outcome measures

Quadriceps volume and Anatomical Cross-Sectional Area

Anatomical cross-sectional area (ACSA) of the rectus femoris of the right leg was determined using B-mode 2-D ultrasonography (Hitachi EUB-6500, probe frequency 7.5MHz) with the subject prone at 45 degrees. Images were captured at the midpoint between greater trochanter and superior aspect of patella on the mid-sagittal plane of the thigh, with minimal pressure applied to the probe to avoid compression of the muscle. Three images were taken with less than 10% variation and mean area was recorded in cm². Angle of pennation was obtained at the same site and was calculated as the angle of fascicle insertion into the deep aponeurosis.

Sequential 2-D images were compiled using electromagnetic tracking, by running the probe the length of the muscle in a transverse orientation. Segmentation was performed manually by drawing around the perimeter of rectus femoris at 5mm slice intervals. To assess the reliability of this method ten randomly selected 3-D scans were selected and re-analysed.

Muscular Strength

Isokinetic strength of the knee extensors was measured bilaterally using a Cybex Norm Isokinetic Dynamometer (Cybex, Rockonkoma, NY). Following familiarization, which was held on a separate visit, patients were seated in a chair and the knee joint was aligned with the axis of rotation of the dynamometer and performed three sets of three maximal extension contractions at angular velocities of 60, 180 and 240°/second. The highest peak torque achieved in newton meters was recorded.

Isometric maximum voluntary contraction was also measured using computerized dynamometry with the leg fixed at a 90°angle. Patients performed three maximal contractions and the highest peak torque in newton meters was recorded.

Exercise Capacity

There are no validated field tests of exercise capacity in the advanced CKD population. We elected to assess walking performance using the incremental shuttle walk test (ISWT), which tests maximal exercise tolerance and the endurance shuttle walk test (ESWT), which tests endurance capacity. These tests have been validated and widely used in chronic obstructive pulmonary disease (COPD),¹¹ and other long term conditions.

Both tests are externally paced and were carried out over a flat 10m course in a hospital corridor. Patients were played standardized instructions and told to walk for as long as possible keeping up with the beeps, if patients slowed their walking speed they were verbally instructed to “catch up”, but no other verbal encouragement was given.

The ISWT is progressive and terminated upon failure to keep up with the pace or volitional exhaustion indicated by the patient. Total distance covered in meters was recorded.

During the ESWT the speed was set to 85% of VO_{2Max} estimated from the ISWT and remained constant. Patients were instructed to walk for as long as they could, or until they could no longer keep up with the set pace. Total time walked for in minutes and seconds was recorded.

Statistical Analysis

All data are presented as mean and standard deviation unless otherwise stated. All continuous outcomes were tested for normality using the Shapiro-Wilk test. If data were found to be non-normally distributed, statistical analysis was performed on log transformed data. Linear regression

models were fitted to test the effect of the exercise intervention on the primary and secondary outcome measures with the change as the dependent variable and the group assignment and baseline value as the covariates. This was performed with a sensitivity analysis to adjust for age, gender, cardiac comorbidity and baseline eGFR, which are all factors that could affect patients ability to gain muscle mass. Within group changes were analysed by paired t tests. Regression modelling was also used to test the relationship between an increase in muscle mass and improvement in secondary outcome measures. Progression of weight lifted each week during training sessions was tested using a one way repeated measures analysis of variance and when appropriate, pairwise comparisons were used to compare within group changes over time. The difference in total weight lifted each session at the beginning and end of the training period was analysed by linear regression. Data were analysed using intention to treat methods; therefore missing follow-up data were imputed using the last observation carried forward method, which assumes that individuals who withdrew or were lost to follow-up had no change from baseline. Any data missing at baseline was imputed as the mean value at baseline across the whole cohort. Reliability of 2-D and 3-D ultrasound scans and angle of pennation analysis was determined using type 3.1 intra-class correlation coefficient (ICC). For 2-D scans this was calculated using the three values obtained for ACSA by one operator: $r=0.99$; for 3-D volume scans and angle of pennation analysis this was calculated from two values obtained during analysis: $r=0.98$ and $r=0.91$ respectively. All statistical analysis was carried out using IBM SPSS 20 software (SPSS, Chicago, IL). Statistical significance was accepted when two-tailed P values were <0.05 .

Results

Recruitment, Retention, Adherence rates and Baseline Characteristics

In total, 403 patients were identified as eligible by consulting doctors and approached with a view to recruitment. 38 patients were randomised in 16 months (approximately 10% uptake rate), a low

recruitment rate compared to others reported in the literature.¹²⁻¹⁴ 33/38 (87%) patients completed the study, with two patients withdrawing/lost to follow-up from the exercise group and three from the non-exercise control group. Reasons for withdrawal included progression of a non-related disease (n=2), family illness (n=1), anxiety about study (n=1) and death (n=1). 18/20 (90%) patients randomised to exercise completed the intervention with 92% attendance rate at training sessions (range 75-100%). Baseline characteristics are shown in Table 1.

Changes in rectus femoris anatomical cross-sectional area and pennation angle

Changes in rectus femoris ACSA are shown in Table 2. Subjects who exercised had a mean increase in ACSA of $0.5 \pm 0.6 \text{ cm}^2$ (8.3%) following eight weeks of resistance training ($P < 0.01$), with no change in the non-exercising controls ($P = 0.90$) giving an overall significant difference between the two groups ($P < 0.01$). This effect remained when ACSA values were adjusted for baseline eGFR which was seen to differ between the groups and could impact upon patients ability to gain muscle mass (Supplementary table 1; $P = 0.02$). There was no difference between the groups in terms of change in fascicle pennation angle ($P = 0.66$).

Changes in rectus femoris volume

Changes in volume of rectus femoris are shown in Table 2. Rectus femoris volume was seen to increase by $15.0 \pm 23.1 \text{ cm}^3$ (9.8%; $P = 0.009$) following resistance exercise training. There was no change in the non-exercising control group ($P = 0.34$), giving a significant difference between the two groups ($P < 0.01$). This effect remained when muscle volume was adjusted for baseline eGFR (Supplementary table 1; $P = 0.025$).

Changes in muscular strength

Changes in muscular strength and results of regression analysis are shown in Table 2. The exercise intervention increased knee extensor strength at 60°/sec ($P<0.001$) and 180°/sec ($P=0.007$) with no change in the non-exercising controls; this resulted in significant differences between the two groups ($P=0.001$ and $P=0.004$ respectively). These effects remained after adjusting for baseline eGFR (supplementary table 1) ($P=0.003$ and $P=0.011$ respectively). Figure 2 shows the weekly progression of total weight lifted in training sessions calculated as weight x repetitions x sets. Exercising patients progressed from lifting a total weight of $912 \pm 440\text{kg}$ to $1600 \pm 946\text{kg}$ per session over the eight week period ($P=0.001$) which demonstrates good adherence to the exercise intervention. No difference between the groups was seen in isometric strength ($P=0.40$).

Changes in exercise capacity

Eight weeks of resistance training led to a significant increase in the EWST duration by 2.4 ± 4.8 minutes ($P=0.04$; Table 3), compared to a non-significant reduction in the non-exercise control group of $2.1 \pm 5.7\text{minutes}$ ($P=0.13$), giving a significant difference between the groups ($P=0.01$). This effect remained after adjusting for baseline eGFR (Supplementary table 1; $P=0.01$). Furthermore, the increase in ACSA and volume were both associated with higher ESWT performance at follow up ($P=0.029$ and $P=0.046$ respectively). There was no difference between groups in the ISWT ($P=0.15$, Table 3), and neither group was seen to significantly change from baseline ($P>0.05$).

Discussion

Feasibility of intervention

The relatively high retention (87%) and adherence rates (92%) demonstrate that this type of exercise programme is acceptable for patients. However, we do need to take into account the slow recruitment rates seen here compared to similar interventions.^{12,15,16} For subsequent larger studies we may need to

consider larger multi centre studies if large patient numbers are required as only 10% of eligible patients approached enrolled in the study. Patients approached in out-patient clinics were generally interested in the study and wanted to participate; however the time and travel commitments prevented a significant number of willing patients from taking part. This suggests that a hospital based out-patient supervised exercise programme is not the most practical method of delivery. An exercise programme delivered as part of clinical practice would need to be more flexible involving home or community based exercise alongside behaviour and lifestyle modification in order to allow people to incorporate it into their lives. While a study with a control group is the strongest in design, it is our experience that patients consent to studies of this nature because they feel they will benefit from taking part. Patients randomised to the control group in this study were disappointed and requested to receive training at the end of the study, and in studies of a longer duration we see much higher attrition rates from the control group.¹⁷ As discussed in a recent review,¹⁸ it can be interpreted as unethical to discourage physical inactivity when it is widely recognised that exercise improves health. By allowing patients to act as their own controls with a period of usual activity preceding the training period, and interpreting observations in an intention-to-treat manner, it overcomes the problem of the exercise intervention only being offered to half of the cohort and may help improve recruitment rates.¹⁸

Effect of Resistance Exercise Training on Functional Outcome Measures

Here we have also reported some preliminary results of the effect of an 8 week progressive resistance exercise programme on muscle size, strength and walking capacity in patients with advanced CKD, which to our knowledge has only been investigated by two previous studies.^{8,9} This study therefore adds new data to an under-researched field that could inform power calculations for future definitive trials.

We found that resistance exercise training resulted in an 8.3% increase in ACSA and 9.8% increase in volume of rectus femoris by ultrasound, supporting the results from previous studies from

haemodialysis patients.^{13,19} To our knowledge, only one other study has investigated the effect of resistance exercise on muscle size in advanced CKD,⁸ which reported an increase in muscle fibre size, supporting the results presented here.

This hypertrophy appears to be functional; there were also significant gains in muscular strength measured isokinetically at angular velocities of 60°/s (13% improvement) and 180°/s (11% improvement), which has been reported previously in the renal population.^{8,13} Although no aerobic exercise was included in the exercise programme patients performed better in the ESWT at follow up, which was associated with the gain in muscle mass. This suggests that muscle wasting and weakness is an important limiting factor for physical functioning in these patients, which has been reported previously in ESRD.¹⁰ The increase in muscle size contributed towards some of the improvement in strength, but does not explain it fully. Other factors could include neurological adaptations and improvements in muscle architecture, for example pennation angle of muscle fibres resulting in greater force production. In the healthy population there is some discrepancy in training-induced changes in pennation angle, some studies describe an increase with training,²⁰ whilst other do not.²¹ To our knowledge, this is the first study to report that progressive resistance exercise does not lead to a change in pennation angle in patients with advanced CKD. This may be because the training load was sufficient to cause an increase in strength and CSA, but not to bring about morphological changes such as changes in pennation angle. It is also possible that any increase in pennation angle was so small that ultrasonography was not sensitive enough to detect it.

Given the specificity of adaptation to training,²² it is unsurprising that no improvement was seen for either isometric strength or higher velocity isokinetic strength as subjects performed low velocity isotonic contractions in training. We also saw no improvement in the distance covered during the ISWT. This suggests that maximal aerobic capacity is not influenced by resistance exercise, but walking mechanics is. However, despite the fact that these shuttle walking tests are used extensively in the COPD population,¹¹ they are yet to be validated in the CKD population. Renal anaemia could be a confounding factor here, but there was no difference between groups in haemoglobin

concentrations either at baseline or after eight weeks. It is possible that this study was not sufficiently powered to detect a significant improvement in ISWT performance. A post-hoc power calculation revealed with 80% power we could detect a 0.45cm² increase in ACSA, a 19.5cm³ increase in rectus femoris volume and 59m improvement in ISWT performance. The study seems to have been sufficiently powered to detect a change in muscle size, but we may have been slightly under powered to detect a change in ISWT performance, which is slightly less sensitive to changes following training than the ESWT.²³

Values for the minimal important clinical difference in muscle mass are not available for this population and therefore it is hard to determine the clinical significance of the increases in volume and ACSA reported here. We know that a larger muscle mass is associated with better clinical outcomes and survival in haemodialysis patients,^{4,24} but it remains unknown if this is the case in the advanced CKD population. It has also been reported that a larger muscle mass is associated with better physical functioning in haemodialysis patients²⁵ and Roshanravan and colleagues²⁶ have recently demonstrated in a cohort of CKD patients' stage 2-4, impaired physical performance was strongly associated with all-cause mortality. This indirect evidence suggests that this improvement in physical functioning could have potentially modified the patient's risk of all-cause mortality, but we do not have the data to support this and more extensive clinical trials are required to investigate this important clinical outcome.

This feasibility study has some limitations which are important to address in future study design. Firstly, there appear to be differences in eGFR at baseline between the two groups and there is a gender imbalance in the control group; there was however, no difference in the rate of change of eGFR over the course of the study and a sensitivity analysis showed that neither baseline eGFR nor gender had any effect on outcome measures (see supplementary table 1). As a small feasibility study we could not stratify for these variables, but this should be addressed in the design of a larger study. Secondly, muscle size was measured by ultrasound, a novel method to evaluate muscle mass in this

population, and not by MRI, which is regarded as the ‘gold standard’ method. However, ultrasound is a reliable method for measuring muscle volume and ACSA,²⁷ and has been shown to correlate well with MR measurements of muscle volume.^{28,29} It is advantageous here, due to faster scan time, more accessible and cheaper than MRI. The same operator performed all the scans with the intra-class correlation coefficient determined at 0.98. This suggests ultrasound could be a valuable tool for assessing muscle mass both clinically and for research purposes. Thirdly, assessor blinding was not possible and experimenter bias may have influenced the results, however standardized instructions and encouragement were given to all patients during exercise testing, so this is unlikely. For a more rigorous study design in the future blinded assessing should be considered. Finally, the lack of a healthy control group in the current study means that no direct comparison can be made in terms of the extent of muscle wasting these patients’ exhibit or decrement in performance of functional tests at baseline. We also cannot draw any conclusions on the extent to the improvement in any of the outcome measures compared to the healthy population. The addition of a healthy control group should be considered in future studies.

Conclusions

This study has demonstrated that an eight week resistance exercise study in patients with advanced CKD is feasible. This is supported by high retention and adherence rates. The results presented here also show that resistance exercise is effective at increasing muscle mass in these patients. This was observed alongside significant increases in muscular strength, and improved endurance walking time. This suggests improving muscle mass could be important for improving physical functioning, which is commonly reduced in these patients, but needs to be confirmed by larger randomised controlled trials. However, exercise programmes delivered with this structure seems appropriate for only a small proportion of our renal population and therefore may not be feasible clinically. Future methods of exercise delivery may need to be more flexible and even home based to allow patients to incorporate it into their lives.

Statement of Competing Financial Interests

None to declare

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Figure Legends

374 Figure 1. Flow of patients through the study.

375 Figure 2. Mean (\pm SEM) progression in the total weight lifted in the last training session of each week.

376 * $P < 0.01$ ** $P < 0.001$ significantly different to baseline.

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Tables

Table 1. Baseline Patient Characteristics

	Exercise Group	Non-Exercise Control Group
<i>N</i>	20	18
Male:Female	11:9	14:4
Age (years)	63 (57–65)	66 (63–72)
Ethnicity White: Indian south Asian	18:2	16:2
BMI (kg/m ²)	32.7 (30.3–38.5)	31.6 (28.1–34.1)
Modified MDRD eGFR (mL/min/1.73m ²)	28.5(19.0–32.0)	20.5 (16.0–26.0)
Systolic Blood Pressure (mmHg)	130 (120-137)	123 (112-134)
Diastolic Blood Pressure	77 (69-80)	68 (60-80)
Haemoglobin (g/dl)	12.0 (11.3–13.0)	12.1 (11.2–13.0)
Albumin (g/L)	43.3 (40.5–45.0)	43.0 (40.0–46.0)
Serum total cholesterol (mmol/L)	4.8 (3.5-5.2)	4.4 (3.6-5.0)
Serum total triglycerides (mmol/L)	1.69 (1.13-1.95)	1.52 (1.26-2.20)
Protein:Creatine ratio (mg/mmol)	115.2 (20.9-263.1)	58.1 (18-160.9)
C-Reactive Protein (mg/L)	<5	<5
Leucocyte count (x 10 ⁹ /L)	7.4 (6.5–8.5)	7.1 (6.5–8.0)

HbA _{1C} (%)	6.8 (6.1-7.4)	7.1 (6.8-7.4)
Comorbidities (%)		
Diabetes	15	27
CVD	20	22
Stroke	10	5
Heart Failure	0	0
PAD	0	5
Cause of renal disease		
Glomerulonephritis	6	1
Vascularitis	4	2
Polycystic kidney disease	1	2
Obstructive uropathy	1	2
Ischemia	0	1
Diabetes	0	1
Amyloidosis	0	1
Institual nephritis	1	0
Myeloma	1	0
Hypertensive nephrosclerosis	0	1
Renovascular disease	1	0
Unknown aetiology	5	7

*Data are reported as median (interquartile range) unless otherwise specified; eGFR = estimated glomerular filtration rate, BMI = Body Mass Index; CVD = cardiovascular disease. PAD = Peripheral Artery Disease.

Table 2. Changes in Rectus Femoris anatomical cross-sectional area (ACSA) and muscle strength of the knee extensors after 8 weeks of exercise or no exercise.

Variable	Mean \pm SD or median (IQR)		Difference (95% confidence interval)	P-value ^a
	Exercise	Non-exercise Control		
Rectus Femoris ACSA (cm ²)				
Baseline	6.0 \pm 1.9	5.6 \pm 1.6		
8 weeks	6.5 \pm 2.0	5.6 \pm 1.5		
Change	0.5 \pm 0.6	0.0 \pm 0.3	0.4 (0.14, 0.76)	0.006
P-value ^b	0.003	0.901		
Rectus Femoris Volume (cm ³)				
Baseline	153.1 \pm 39.3	146.5 \pm 33.5		
8 weeks	168.1 \pm 48.9	142.4 \pm 33.5		
Change	15.0 \pm 23.2	-4.1 \pm 17.9	19.07 (5.08, 33.06)	0.009
P Value ^b				
Angle of Pennation (°)				
Baseline	9.6 (9.5-10.5)	9.5 (8.7-9.7)		
8 weeks	9.6 (9.2-10.3)	9.6 (9.0-10.2)		
Change	0.0 \pm 0.5	0.1 \pm 1.0	-0.1(-0.67, 0.43)	0.662
P-value ^b	0.721	0.530		

Isometric Strength (Nm)				
Baseline	118.1 ± 54.8	121.0 ± 61.7		
8 weeks	124.2 ± 55.6	123.1 ± 63.7		
Change	6.1 ± 15.1	2.2 ± 13.1	3.91 (-5.59, 13.41)	0.409
P-value ^b	0.085	0.488		
Isokinetic Strength 60°/sec (Nm)				
Baseline	92.6 ± 34.2	99.8 ± 52.6		
8 weeks	104.6 ± 36.8	97.1 ± 24.2		
Change	12.0 ± 12.4	-2.8 ± 10.7	14.81 (6.99, 22.63)	<0.001
P-value ^b	<0.001	0.294		
Isokinetic Strength 180°/sec (Nm)				
Baseline	58.8 ± 30.5	61.4 ± 33.4		
8 weeks	65.3 ± 32.9	59.7 ± 34.9		
Change	6.6 ± 9.8	-1.7 ± 6.2	8.35 (2.84, 13.86)	0.004
P-value ^b	0.007	0.263		
Isokinetic Strength 240°/sec (Nm)				
Baseline	52.8 ± 29.7	52.1 ± 29.7		
8 weeks	54.6 ± 28.4	49.8 ± 29.0		
Change	1.8 ± 7.9	-2.3 ± 5.9	4.12 (-0.40, 8.63)	0.073
P-value ^b	0.318	0.116		
Total weight lifted during training sessions (Kg)				
Baseline	907 ± 441	N/A		

8 weeks	1526 ± 935	N/A		
Change	620 ± 680	N/A		0·001
p-value ^b	<0.001			

414 ACSA – Anatomical cross-sectional area; SD=standard deviation

415 ^a P-values compare the change in the intervention and control groups and were estimated using
416 regression models.

417 ^b P-values test whether the within group change is equal to zero and were estimated using paired t-
418 tests or Wilcoxon signed rank test as appropriate.

419 Table 3. Effect of eight weeks of resistance exercise or no exercise on walking performance in the
420 incremental shuttle walk test (ISWT) and the endurance shuttle walk test (ESWT).

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	Mean ± SD or median (IQR)			
Walking test	Exercise	Non-exercise Control	Difference (95% confidence interval)	P-value ^a
ISWT (m)				
Baseline	385.0 (197.5-520.0)	330.0 (180.0-420.0)		
8 weeks	340.0 (237.5-552.5)	290.0 (125.0 - 460.0)		
Change	23·5 ± 69.4	-10·6 ± 55.4	29.29 (-11.40, 69.97)	0·153
P-value ^b	0.146	0.430		
ESWT (mins)				
Baseline	5.83(3.86-18.67)	7.2 (3.30-19.53)		
8 weeks	11.42(4.89-20.00)	5.36(4.24-10.67)		
Change	2·4 ± 4.8	-2·1 ± 5.7	4·29 (1.05, 7.53)	0·011
p-value ^b	0.038	0.136		

422 SD=standard deviation

^a P-values compare the change in the intervention and control groups and were estimated using regression models adjusted for baseline value.

^b P-values test whether the within group change is equal to zero and were estimated using paired t-tests.

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