12-weeks combined resistance and aerobic training confers greater benefits than aerobic alone in non-dialysis CKD

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Abstract

There is a growing consensus that chronic kidney disease (CKD) patients should engage in regular exercise, but there is a lack of formal guidelines. In this report, we determined whether combined aerobic and resistance exercise would elicit superior physiological gains, in particular muscular strength, compared to aerobic training alone in non-dialysis CKD.

Non-dialysis CKD patients stage 3b-5 were randomly allocated to aerobic exercise (AE, n=21; 9 males; median age 63years [IQR, 58-71]; median eGFR 24[IQR, 20-30] mL/min/1.73m^2) or combined exercise (CE, n=20, 9 males, median age 63years [IQR, 51-69], median eGFR 27[IQR, 22-32] mL/min/1.73m^2), preceded by a 6-week run in control period. Patients then underwent 12-weeks of supervised AE (treadmill, rowing or cycling exercise) or CE training (as AE plus leg extension and leg press exercise) performed 3x/week. Outcome assessments of knee extensor muscle strength, quadriceps muscle volume, exercise capacity and central haemodynamics were performed at baseline, following the 6-week control period and at the end of the intervention.

AE and CE resulted in significant increases in knee extensor strength of 16±19% (P=0.001) and 48±37% (P<0.001) respectively, which were greater after CE (P=0.02). AE and CE resulted in 5±7% (P=0.04) and 9±7% (P<0.001) increases in quadriceps volume respectively (P<0.001) which was greater after CE (P=0.01). Both AE and CE increased distance walked in ISWT (28±44m; P=0.01 and 32±45m P=0.01) respectively.

In non-dialysis CKD, the addition of resistance exercise to aerobic exercise confers greater increases in muscle mass and strength than aerobic exercise alone.

Key words: Chronic Kidney Disease, Exercise, Strength, Skeletal Muscle, Physical Function.

Introduction

Chronic Kidney Disease (CKD) patients exhibit skeletal muscle wasting and reduced muscular strength, physical function, and cardiorespiratory fitness, resulting in elevated cardiovascular risk. These are important modifiable risk factors associated with increased morbidity and mortality, reduced quality of life and increased risk of falls (18, 21, 23).

Whilst international guidelines have begun to highlight that CKD patients should engage in exercise (14, 20), specific advice is not given and there is a lack of evidence from randomised controlled trials to underpin the guidance offered. Resistance exercise can increase muscle size, function (26), and metabolism (25), while aerobic exercise (AE) confers cardiovascular benefits, such as aerobic capacity improvements and cardiac protection (16). Ideally, a combination of these exercise modalities would be used in one session to maximise benefits received, but the effect of combining these modes of exercise has not been fully studied in non-dialysis CKD. This is particularly important because the effects of AE on skeletal muscle remain equivocal. Our previous research has shown in the absence of additional acidosis correction, AE depletes intramuscular amino acid stores, including reductions in leucine (27), which has well documented anabolic effects (6, 7, 22). This may have negative implications for protein synthesis rates and may compromise gains in muscle mass if the effect persists when exercise modalities are combined.

This study investigated whether 12-weeks of combined aerobic and resistance exercise (CE) would confer greater adaptations in muscle mass and strength compared to AE alone in non-dialysis CKD. It aimed to determine if, when exercise modalities are combined, patients receive improved cardiorespiratory fitness and cardiac function together with increased muscle mass

and strength. This will inform the most appropriate way to deliver rehabilitation programmes for CKD.

Material and Methods

Study Design and Participants

This was a parallel randomized controlled trial where participants acted as their own control by means of a six-week run-in control period prior to randomization. During this time participants were asked to maintain habitual physical activity. Participants were randomized, using a random block method stratified for CKD stage, to either 12-weeks 3x/week supervised CE, or AE alone. Outcome assessments were performed at baseline, at the end of the control period, and at the end of the 12-week intervention.

54 non-dialysis patients with CKD stages 3b-5 were recruited from nephrology outpatient clinics at the Leicester General Hospital, UK, from December 2013 to April 2016 with the intervention period completed in October 2016. Exclusion criteria included: age <18 years, physical impairment sufficient to prevent undertaking the intervention, recent myocardial infarction, unstable chronic conditions, or an inability to give informed consent, and a BMI >40 (due to difficulties in muscle size measurement). Diabetic patients were included if haemoglobin A_{1C} was <9%. The study was given favourable ethical opinion by the National Research Ethics Committee (Ref: 13/EM/0344). All patients gave written informed consent and the trial was conducted in accordance with the Declaration of Helsinki. This study is registered with the ISRCTN (Ref: 36489137).

Exercise Intervention

Patients attended supervised exercise sessions 3x/week for 12 weeks. The AE component consisted of circuits with the exact exercise performed (treadmill, cycling, rowing) chosen by the exercise trainer and patient together. Patients aimed to undertake 30 minutes of exercise at a moderate intensity corresponding to 70-80% heart rate maximum, obtained during a maximal exercise tolerance test (described below), although periods of rest were taken if required. Exercise intensity was monitored continuously throughout each session using heart rate telemetry (Polar Team, Polar Electro Ltd, UK) and rating of perceived exertion 12-14 ("somewhat hard"). Frail and unconditioned patients gradually built up to this target over the 12-week period. For those patients randomised to CE, the resistance exercise component was performed on two out of three sessions each week. On these two sessions, to ensure matched session duration, only 20 minutes of AE was performed. Resistance exercise consisted of leg extension and leg press exercises performed on fixed resistance machines (Technogym, Italy). During baseline assessments, patients performed a 5-Repetition Maximum (5-RM) test on the leg extension equipment. This was the maximum amount of weight that the patient could lift no more than five times in good form with 2-3 minutes rest between successive attempts. Established equations were used to predict estimated 1-Repetition Maximum (e-1RM) (2). The training load (in kilograms, kg) was set at 70% e-1RM and patients performed 3 sets of 12-15 repetitions. An appropriate starting load for the leg press exercise was estimated given leg extension performance, and modified accordingly. Encompassing the progressive overload principle, training loads were increased when patients could comfortably complete three sets with good form.

Outcome Measures

Muscular Strength

Following familiarization, leg extension strength was measured using the 5-RM test described above. The load participants lifted in training sessions calculated as weight x repetitions x sets was recorded to track progression.

Quadriceps Muscle Volume

Magnetic Resonance Imaging (MRI) scans of the right quadriceps were acquired in a 3T Siemens Skyra HD MRI scanner. Images of the entire thigh (from the proximal border of the patella to the superior aspect of the femur) were obtained in the axial plane using a T1 turbo spin-echo sequence with the following parameters: slice thickness=5mm with no gap between slices; repetition time/echo time=873ms/14ms; field of view=450x309.4mm; in-plane resolution=0.879x0.879mm. Volume was measured on 10mm thick slices by manually outlining the facial boundary of each muscle from the first distal slice where rectus femoris (RF) was visible and every slice thereafter until the most proximal slice where vastus medialis was visible, using Jim online imaging analysis software (Xinapse Systems, UK).

Rectus Femoris Anatomical Cross-sectional Area

Anatomical cross-sectional area (ACSA) of RF of the right leg was determined using B-mode 2D ultrasonography (Hitachi EUB-6500; probe frequency, 7.5 MHz) with the patient prone at 45°. Images were captured at the midpoint between the greater trochanter and superior aspect of the patella on the midsagittal plane of the thigh, with minimal pressure applied to the probe to avoid compression. Three images were taken with <10% variation and mean area in cm^2 was recorded. The researcher performing the ultrasonography was blinded to baseline values to prevent bias in image interpretation. The same operator performed all scans with an interclass correlation coefficient of 0.95.

Exercise Capacity

Cardiorespiratory Fitness

Peak exercise capacity (VO_{2peak}) was determined during an incremental Cardiopulmonary Exercise Test (CPET) performed on an electrically-braked cycle ergometer (Lode Excalibur Sport, Gronigen, Netherlands). Following a 3-minute warm up at 30W, fly wheel resistance increased by 1W every 3 seconds in a ramp protocol (17). Throughout the test, electrocardiogram output, blood pressure and heart rate were recorded continuously and reviewed by a cardiac nurse or doctor. The test was stopped if RPM <60 and was unable to be increased, the patient reached volitional exhaustion, or under the advice of the cardiac specialist. Breath-by-breath measurement of oxygen consumption (Cortex MetaLyzer, Cranlea, UK) was performed to determine oxygen consumption. Absolute (L/min) and relative VO_{2peak} (ml/kg/min) were calculated over a rolling 20 second average.

Walking capacity

Walking capacity was assessed using the 10m progressive incremental shuttle walk test (ISWT) (26). Patients were played standardized instructions and asked to walk for as long as possible keeping up with the externally paced beeps. The ISWT was terminated upon failure to maintain the required pace, or volitional exhaustion. Total distance covered in meters was recorded. Assessments were performed following familiarization of the protocol.

Cardiac Bioreactivity

Resting central haemodynamics including heart rate, stroke volume, cardiac output and total peripheral resistance were measured using non-invasive cardiac monitoring (NICOM, Cheetah Medical Inc. USA). Four electrodes were placed on the thorax and patients were fitted with a

blood pressure (BP) cuff. Patients sat for 20 minutes, during which time BP and mean arterial pressure (MAP) were measured every five minutes, and cardiac output (CO), stroke volume (SV), and total peripheral resistance (TPR) were measured every three-five seconds. To ensure a true resting sample, data from the first five minutes of the test was disregarded and mean values were calculated from the remaining 15 minutes. In addition, body size adjusted indexes of cardiac index and total peripheral resistance index (TPRI) were calculated.

Statistical Analysis

Data is presented as mean ± standard deviation and data related to change are presented as mean and 95% confidence intervals. The primary purpose of this study was to generate skeletal muscle biopsy samples to extend our previous work (27, 28). As such, this study was powered on a training load to elicit a detectable physiological response following exercise. To ensure such appropriate response, we required a minimum sample of 21 patients (80% power, α=0.05). This was based on our previous work (26) where by a 75% (600±682kg) increase in weight lifted in a single training session was seen over the course of the study. To ensure matched groups, 21 patients were also recruited into the AE only group, and to allow for a 30% dropout rate, 54 patients (27 in each group) were recruited.

All data was tested for normality using the Shapiro-Wilk test. If data was not normally distributed, analysis was performed on the log transformed data, or non-parametric tests were used as appropriate. Baseline characteristics were compared using independent samples t-tests. The six-week control period was analysed by paired sample t-tests as this was prior to randomization. Within-group changes over time were analysed by paired sample t-tests, or Wilcoxon signed-ranks test as appropriate, and linear regression models were fitted to

determine between group differences with the change as the dependent variable and the group assignment, baseline value, age, gender, haemoglobin and diabetes as co-variants. Regression modelling was used to test the relationship between an increase in muscle mass and improvement in secondary outcome measures and the relationship between disease severity and improvement in outcome measures. Differences in the weight lifted between the first and last training session was analysed using paired samples t-tests. Missing data was analysed using Little's test, to test the assumption of missing completely at random (MCAR). This showed that missing data was MCAR and so a complete case analysis was performed as, although this reduces the power of the study, it does not bias the results (29). A sensitivity analysis was performed using intention-to-treat methods, whereby missing data from randomized participants was imputed using last-observation-carried forward to confirm the results from the complete case analysis (24). This method of imputation was chosen because of its conservative P value estimate. There was complete agreement for all variables using the two methods, therefore data is presented as a complete case analysis. Statistical analysis was carried out using IBM SPSS 25 software (IBM, Chicago, IL). Statistical significance was accepted as $P<0.05$.

Results

Baseline Characteristics, Recruitment, Retention and Adherence Rates

Patient characteristics can be found in Table 1 and the CONSORT diagram in Figure 1. Apart from a higher plasma albumin level in AE (P=0.01), the two groups were well matched. 483 patients were identified as eligible by medical staff and approached for recruitment, of which 429 patients declined and 54 patients consented. This 11% uptake is comparable to our earlier report (26). 13 patients were excluded during the six-week control period due to: voluntary withdrawal, treatment for associated medical conditions, and positive changes on ECG during CPET test. We saw high retention once exercise training had begun with 85% of AE and 90% of CE groups completing the training period and an average 88% attendance at training sessions in both groups.

Control Period

Apart from e-1RM, there was no change seen in any variable over the control period (Table 2).

Muscular Strength

The total weight lifted in the CE group increased from 895±408kg to 1510±658kg over the duration of the study (P=0.001). This exceeds the 600kg increase required to elicit a physiological adaptation from our power calculation. Changes in knee extensor strength measured by e-1RM are shown in Table 3 and Figure 2. Mean increases of 9kg (P=0.001) and 22kg (P<0.001) were seen in the AE and CE groups respectively. The gains achieved by patients performing CE were superior to those made by the patients in the AE group (+13kg P=0.02) (Table 3 and Figure 2).

Quadriceps Muscle Volume

A mean increase of 40.5cm^3 (5.1%) *P*=0.04) was seen following AE, compared to a mean increase of 88.0cm^3 (9.4%) (*P*<0.001) following CE. When accounting for differences in the presence of diabetes, haemoglobin, age, gender and baseline quadriceps volume, the magnitude of change was 47.5cm^3 (*P*=0.01) greater in those performing CE (Table 3 and Figure 3).

Rectus Femoris ACSA

There was a significant increase in RF ACSA following CE (+0.7cm^2, 9.7%, *P*<0.001) but not AE (+0.4cm^2, 3.5%, *P*=0.1). Despite numerically larger gains seen in the CE group (+0.4cm^2), this was not significantly greater than the AE group (*P*=0.3) (Table 3).

Exercise Capacity

Cardiorespiratory Fitness

Changes in parameters collected during the CPET test are shown in Table 3. Small non-significant gains were seen in relative VO_{2Peak} in both groups (AE: +1.1ml/kg/min, 5.1%, *P*=0.4; CE: +0.6ml/min/kg, 3.1%, *P*= 0.4). Peak power was significantly greater following 12 weeks of CE (+8W, *P*=0.04) with no improvement seen in the AE group (+9W, *P*= 0.1). This increase could not be attributed to changes in muscle size (r^2=0.07) or strength (r^2=0.04). There was no difference in the improvements made between the groups (*P*=0.3).

Exercise Capacity

A significant improvement was seen in the distance covered during the ISWT after training in both groups (AE: +28m, 6.1%, *P*=0.01; CE: +32m, 9.8% *P*=0.01), with no difference between groups (*P*=0.8) (Table 3).

Cardiac Bioreactivity

Changes in cardiac bioreactivity measures can be found in Table 4. Blood pressure was reasonably controlled at baseline 142.9±20.0 mmHg / 80.9±7.0mmHg and did not change after training in either group. TPR and TPRI increased following CE (+86.9 dyne/s/cm^5 *P*=0.04 and +172 dyne/s/cm^5/m^2, *P*=0.04 respectively), but this was not seen in the AE group (*P*=0.5 and *P*=0.03). There was no change seen following training in either group for MAP, SV, SVI, CO, or cardiac index.

Relationship with disease severity

There was no relationship between eGFR and the change in any of the outcome measures included in our analysis in either group (data not shown) suggesting that disease severity did not interfere with the patient's ability to adapt to an exercise programme.

Discussion

Despite a growing consensus that CKD patients at all stages should engage in some form of regular exercise (8, 12, 13, 16, 31), no formal exercise guidelines exist. It is advised that patients perform both resistance and AE to gain benefits for muscle mass and strength as well as improvements in cardiorespiratory fitness and a reduction in cardiovascular risk (16, 26). For time and logistical reasons, combining both modes in the same session would be optimal. However, previous evidence from our group suggests that AE may reduce stores of essential amino acids, in particular leucine (27), which could have important implications for protein synthesis rates and hypertrophy. This report describes the effect of 12-weeks of CE compared to AE alone on muscle size and strength, and exercise capacity. This data will help to inform exercise recommendations for CKD patients and provides pilot data for future randomized controlled trials.

Both AE and CE groups exhibited significant improvements in knee extensor strength measured by e-1RM of 9 and 22kg respectively. The gains (49% increase) seen in the CE group were significantly larger than those achieved by the AE group, but given the specificity of resistance training is unsurprising. Whilst this increase is similar to that reported by Castaneda and colleagues (4), who reported 12 weeks of resistance training resulted in a 47% increase in knee extensor strength measured by 1-RM, it is larger than the 13% improvement in isokinetic knee extensors strength (at an angular velocity of 60°/second) previously reported in this population by our group (26). It is likely that the differences in assessment of strength account for the discrepancies in its improvement.

We have shown that 12-weeks of CE resulted in a significant 9.4% increase in quadriceps volume, with smaller gains seen in the AE group. The gains achieved with CE are comparable to those previously reported (9.4%) following eight-weeks resistance exercise using the same training and in the same population (26). It is important to highlight that 12 weeks of aerobic exercise performed three times a week was sufficient to significant improve muscular strength in this patient group. Despite not reaching statistical significance, patients in the AE group still achieved a 5% increase in quadriceps volume and a 3.5% increase in RF ACSA. Significant improvements in lean body mass of 2.3%, measured by DXA, have been reported previously following 12-weeks treadmill AE (1). This demonstrates that in deconditioned patients, weight bearing exercise alone can produce some improvement in muscle size and strength. Taken together, these data suggest that the addition of resistance exercise to AE confers greater increases in muscle mass and strength in CKD than AE alone. Therefore, combining both modes of exercise together, as in a rehabilitation class for example, still confers benefits for muscle mass, so long as the overload stimulus is sufficient.

Cardiorespiratory fitness is frequently reported to be lower in CKD patients compared to healthy counterparts (12, 13) and the values reported here are much lower than predicted values(19). Although we saw no statistically significant improvements in VO_{2Peak} in either group following 12-weeks of exercise, with improvements of 5% after AE and 3% after CE, which remained after controlling for the presence of anaemia, the changes are consistent with two large systematic reviews in which pooled mean aerobic capacity improved significantly following exercise training in non-dialysis CKD (12, 13). Given the sample sizes (n=847-928) of these meta-analyses, our study could be underpowered to detect such a change. Larger changes may have been seen with a longer intervention period. For example, Headley and colleagues saw a significant 8% improvement in VO_{2Peak} following 48-weeks of AE (11), whilst Greenwood and colleagues reported a 14% improvement in VO_{2Peak} following 12-

months of supervised rehabilitation classes (9). We did however, report an increase in the maximum power output achieved during the CPET test in the CE group, which could not be attributed to either the increase in muscle size or strength. Alongside modest improvements in cardiorespiratory fitness, we observed an improvement in walking ability in both groups as determined by greater distances covered in the ISWT.

Finally, BP, MAP, SV, and CO remained unchanged by either mode of exercise. TPR and TPRI were both seen to significantly increase following CE, which may reflect a worsening of endothelial dysfunction that was not seen with AE alone. Previously we found that six-months of walking exercise in non-dialysis CKD protects cardiovascular function (16). This effect of resistance exercise on haemodynamics warrants further investigation. Unfortunately we were not able to reliably extract information about medication from patient's medical notes. Information on prescription of anti-hypertensives would be critical in the full interpretation of the data on blood pressure and TPR presented here. This means we are unable to conclude if there was any improvement in blood pressure control as the dose of anti-hypertensives may have reduced over the course of the study.

Several studies have now been published describing the association of reduced physical function and muscle wasting with poor outcomes and an increased risk of mortality (3, 10, 15, 18, 21, 23). Therefore any intervention that is able to impact upon either of these factors is likely to improve patient outcomes and reduce health care-usage. However, as no health and socio-economic analysis was performed here this cannot be inferred. This would be an important assessment to make to encourage clinical adoption of such an intervention.

Disappointingly we only recruited 11% of the patient who were approached, however, we did have high retention (CE 85%, AE 90%) and attendance rates (88% in both groups), suggesting that exercise training delivered in this way is acceptable for a small proportion of the population. Reasons for non-recruitment were not formally collected, but patients frequently mentioned time commitments and frequent travel to the hospital as significant barriers to participation. The outcome measure protocol involved in this study, including muscle biopsies and MRI scans as well as a range of physiological measures, was fairly onerous and discouraged many patients. This is not a "real life" effectiveness trial and therefore cannot indicate the feasibility of supervised exercise training delivered as part of a clinical service. However, supervised hospital-based training may not be a practical lifestyle choice for the majority of the renal population and future research should focus on delivery of such interventions in the community where uptake may be enhanced, or strategies to encourage self-directed exercise behaviour (5).

Given the low adaptation rate of the intervention seen here we should be cautious about the generalisation of the results to the renal population as a whole. It is possible that we have recruited the fittest and healthiest patients here and whether these results apply to a more elderly and frail population is unclear.

One of the main limitations of this study is the lack of a non-exercising control group, which was excluded to promote recruitment. However, we feel this limitation is negotiated the 6-week control period, where we observed no changes during this period, apart from e-1RM which increased by 3kg. However, this increase falls below the minimal detectable difference (6kg) and may simply be due to inherent error/variation in this test (30). The lack of a resistance training only group means that unfortunately we are not able to draw any firm conclusions about the most suitable training programmes for patients to undertake. This arm to the study was omitted as we have previously performed a randomised controlled trial of resistance

exercise training in this population (26) and reported similar improvements in muscle mass and strength to those seen here. It was also excluded it to ensure successful recruitment in a heavily researched patient population. The study design may also be limited by the difference in AE duration performed by the groups. In the two sessions including resistance exercise, only 20 minutes of AE was performed to ensure approximately 30 minutes of total exercise and to pragmatically match all sessions for duration. As such, it may be that the total of 4 hours (i.e. 20 minutes less/week X 12-weeks) of reduced aerobic component performed by the CE group precluded greater improvements in aerobic-based parameters. As planned, our trial was adequately powered to elicit physiological hypertrophic responses in the muscle, however it was not powered for other outcomes. The non-significant improvements observed should be investigated further.

In conclusion, the addition of resistance exercise to AE confers greater increases in muscle mass and strength in CKD than AE alone. This suggests that non-dialysis CKD patients should be encouraged to include resistance training in exercise programmes to maximise the benefits. However, given the poor uptake of this hospital-based programme, future studies need to effectively investigate incorporating resistance exercise into home or community-based interventions for non-dialysis CKD.

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Conflict of interest statement

The authors declare they have no other relevant financial interests or any conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format. Some of the data contained herein has been presented in abstract form at the American Society of Nephrology, Chicago, 2016 and the ERA-EDTA, Madrid, 2017.

Author Contributions

My co-authors have all contributed to this manuscript and relative contributions made by the listed authors are as follows: Research idea: EW, JV, AS; data acquisition: EW, DG, AC, BV, JV, SX, TW; data analysis and interpretation: EW, DG, SX, TW; statistical analysis; EW, DG, SX, TW; supervision or mentorship: AS. Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuing that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Tables

Table 1. Baseline patient characteristics

	AE group	CE group	*P*
Number of patients	21	20	
Number of Males	9	9	
Age (y)	63 (58-71)	63 (51-69)	0.36
Ethnicity **White** **Indian/South Asian** **Black Caribbean**	 15 4 2	 11 9 0	
BMI (kg/m^2)	29 (25.5-35.5)	29.5 (25.5-33.0)	0.47
eGFR (mL/min/1.73m^2)	24 (20-30)	27 (22-32)	0.92
Systolic blood pressure (mm Hg)	135 (122-145)	125 (120-132)	0.15
Diastolic blood pressure (mm Hg)	73 (68-81)	70 (72-78)	0.57
Haemoglobin (g/dL)	119 (115-131)	112 (105.5-128.5)	0.06
Albumin (g/L)	42 (41-44)	40.5 (38.5-42)	0.01
Serum total cholesterol (mmol/L)	4.4 (3.7-4.8)	3.6 (3.5-3.9)	0.13
Serum total triglycerides (mmol/L)	1.6 (1.2-2.2)	1.3 (1.0-2.1)	0.51
C-Reactive protein (mg/L)	29.5 (19.5-39.2)	6 (6-6)	0.34*
Leukocyte count (x10^9/L)	7.8 (6.8-8.3)	7.3 (6.5-8.8)	0.54
Haemoglobin A_{1c} (%)	6.3 (5.6-7.5)	5.8 (5.5-5.9)	0.27
Comorbid conditions **Essential hypertension** **Diabetes** **IHD** **Heart failure** **Valvular disease** **Stroke** **PAD**	 10 7 1 0 1 0 0	 12 2 2 1 0 0 1	
Godin LTEQ	34.0 (20.1-47.9)	21.0 (7.7-34.3)	.174

Note: Unless otherwise indicated, values for categorical variables are given as number, values for continuous variables as median, [interquartile range].

Abbreviations: AE, Aerobic exercise; BMI, body mass index; CE, Combined exercise; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IHD, Ischemic Heart Disease; PAD, peripheral artery disease; Godin LTEQ, Godin Leisure Time Exercise Questionnaire. * CRP values were only available for AE n=4; CE n=7

Table 2. Change in outcome measures over 6-week control period

Variable	Baseline	6-Weeks	*P*
Quadriceps volume (cm^3)	949.3 ± 320.7	935.5 ± 315.5	0.2
Rectus Femoris ACSA (cm^2)	8.4 ± 2.6	8.7 ± 2.9	0.2
e-1RM (kg)	47 ± 22	50 ± 23	0.04
ISWT (m)	407 ± 194	418 ± 195	0.2
ESWT (min)	11.1 ± 6.9	12.7 ± 7.5	0.1
$VO_{2\ Peak}$ (ml/kg/min)	20.1 ± 5.3	20.4 ± 5.6	0.8
Peak Power (W)	119 ± 42	118 ± 41	0.7
Max HR (bpm)	143 ± 19	137 ± 21	0.2
SBP (mmHg)	139 ± 17	138 ± 18	0.7
DBP (mmHg)	81 ± 8	82 ± 9	0.2
MAP (mmHg)	101 ± 9	101 ± 11	0.1
TPR (dyne/s/cm^5)	1462 ± 471	1397 ± 446	0.7
TPRI (dyne/s/cm^5/m^2)	2676 ± 574.6	2615 ± 692	0.7
SV (mL)	90.0 ± 21.8	90.7 ± 21.0	0.4
SV Index (UNITS)	48.0 ± 6.4	48.4 ± 7.7	0.8
CO (L/min)	6.0 ± 1.0	6.1 ± 1.5	0.8
Cardiac Index (L/min/m^2)	3.3 ± 0.5	3.3 ± 0.7	0.8

Note: Unless otherwise indicated data are given as mean and CI.

Abbreviations: ACSA, anatomical cross-sectional area; CI, confidence interval; CO, cardiac output; DBP, diastolic blood pressure; e-1RM, estimated 1-repetition maximum for knee extensor strength; ESWT, endurance shuttle walk test; HR, heart rate; ISWT, incremental shuttle walk test; MAP, mean arterial pressure; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; TPRI, total peripheral resistance index.

P values test the within-group changes and were estimated using paired *t* tests.

Table 3. Changes in muscle mass, strength and cardiorespiratory fitness over 12-week training period.

Variable	AE	CE	Difference (95% CI)	*P*[a]
weight lifted / session(kg)	n/a	n=18	n/a	
Baseline		895 ± 408		
Post Exercise		1510 ± 658		
Change		615 ± 486		
***P*[b]**		0.001		
e1-RM (Kg)	n=17	n=16		
Baseline	54 ± 27	45 ± 16		
Post Exercise	63 ± 26	67 ± 22	13 (5 – 21)	0.02
Change	9 (5 – 14)	22 (16 – 29)		
***P*[b]**	0.001	<0.001		
Muscle Volume (cm^3)	n=15	n=16		
Baseline	939.0 ± 344.8	932.2 ± 269.9		
Post Exercise	979.5 ± 355.5	1020.2 ± 329.0	47.5 (-5.7 – 100.7)	0.01
Change	40.5 (2.7 – 78.3)	88.0 (47.6 – 78.3)		
***P*[b]**	0.04	<0.001		
RF-ACSA (cm^2)	n=17	n=18		
Baseline	8.6 ± 3.0	8.3 ± 2.7		
Post Exercise	9.0 ± 3.2	9.0 ± 2.7	0.4 (-0.1 – 0.9)	0.3
Change	0.4 (-0.1 – 0.9)	0.7 (0.4 – 1.1)		
***P*[b]**	0.1	<0.001		
ISWT (m)	n=18	n=17		
Baseline	454 ± 194	380 ± 195		
Post Exercise	482 ± 190	417 ± 195	2 (-30 – 33)	0.8
Change	28 (6 – 50)	32 (9 – 56)		
***P*[b]**	0.02	0.01		
VO_{2Peak} (L/min)	n=15	n=17		
Baseline	1.8 ± 0.6	1.5 ± 0.4		
Post Exercise	1.9 ± 0.5	1.6 ± 0.4		
Change	0.1 (-0.2 – 0.04)	0.02 (-0.2 – 0.1)	-0.9 (-0.2 – 0.1)	0.6
***P*[b]**	0.2	0.7		
VO_{2Peak} (ml/kg/min)	n=15	n=17		
Baseline	21.4 ± 6.4	19.5 ± 4.7		
Post Exercise	22.5 ± 6.6	20.1 ± 5.0	-0.7 (-3.0 – 1.8)	0.7
Change	1.1 (-0.3 – 2.4)	0.6 (-1.2 – 2.5)		
***P*[b]**	0.1	0.4		

Peak Power (W)	n=15	n=17		
Baseline	129 ± 48	111 ± 32		
Post Exercise	138 ± 42	119 ± 37	-1 (-13 – 12)	0.3
Change	9 (-2 – 19)	8 (0.3 – 16)		
***P*[b]**	0.1	0.04		
Maximum HR (bpm)	n=15	n=17		
Baseline	142 ± 24	134 ± 19		
Post Exercise	143 ± 12	140 ± 29	17 (-23 – 57)	0.05
Change	1 (-12 – 9)	4 (-15 – 8)		
***P*[b]**	0.8	0.5		

Note: Unless otherwise indicated, values are given as mean and CI.

Abbreviations: AE, aerobic exercise; CE, combined exercise; e-1RM, estimated 1-repetition maximum for knee extensor strength; ESWT, endurance shuttle walk test; RF-ACSA, rectus femoris anatomical cross-sectional area; ISWT, incremental shuttle walk test.

[a]*P* values compare changes in the intervention and control groups and were estimated using regression models.

[b]*P* values test the within-group changes and were estimated using paired *t* tests or Wilcoxon signed-ranks test as appropriate.

Table 4. Changes in haemodynamics over the 12-week training period.

Variable	AE	CE	Difference (95% CI)	*P*[a]
SBP (mmHg)	n=15	n=16		
Baseline	142.9 ± 20.0	136.2 ± 13.9		
Post Exercise	137.9 ± 20.0	138.4 ± 17.4	-6.4 (-4.2 – 16.9)	0.2
Change	-4.9 (-3.1 – 12.9)	2.2 (-9.3 – 5.0)		
***P*[b]**	0.2	0.5		
DBP (mmHg)	n=15	n=16		
Baseline	80.9 ± 7.0	81.8 ± 9.4		
Post Exercise	79.3 ± 8.9	84.0 ± 8.6	4.0 (-1.5 – 9.4)	0.1
Change	-1.5 (-2.6 – 5.8)	2.2 (-6.6 – 2.3)		
***P*[b]**	0.4	0.3		
MAP (mmHg)	n=15	n=16		
Baseline	101.4 ± 9.5	100.1 ± 8.6		
Post Exercise	98.0 ± 10.6	103.8 ± 11.7	6.7 (-0.4 – 13.8)	0.1
Change	-3.4 (-1.6 – 8.5)	3.7 (-9.3 – 1.9)		
***P*[b]**	0.07	0.3		
TPR (dyne/s/cm^3)	n=15	n=16		
Baseline	1561.8 ± 472.4	1368.4 ± 465.7		
Post Exercise	1334.9 ± 480.1	1455.3 ± 417.9		
Change	-227.0 (-58 - 512)	86.9 (-173.0 – 0.8)	-243 (-13.4 – 500.6)	0.9
***P*[b]**	0.3	0.04		
TPRI (dyne/s/cm^3/m^2)	n=15	n=16		
Baseline	2809 ± 758	2433 ± 592		
Post Exercise	2581 ± 528	2605 ± 517	214 (-93 – 521)	0.5
Change	-227 (-149 – 603)	172 (-328 – 16)		
***P*[b]**	0.5	0.03		
SV (mL)	n=15	n=16		
Baseline	84.9 ± 18.4	94.7 ± 24.3		
Post Exercise	89.1 ± 21.3	92.2 ± 21.3		
Change	4.1 (-12.1 - 3.9)	-2.5 (-2.7 – 7.8)	-4.9 (-13.9 – 4.1)	0.8
***P*[b]**	0.3	0.3		
SV Index (UNITS)	n=15	n=16		
Baseline	48.9 ± 10.7	48.0 ± 6.2		
Post Exercise	50.0 ± 7.2	48.6 ± 8.8	-0.6 (-5.2 – 4.0)	0.9
Change	0.8 (-3.8 – 5.1)	0.4 (-2.6 – 3.4)		
***P*[b]**	0.8	0.8		

CO (L/min)	n=15	n=16		
Baseline	5.6 ± 1.2	6.5 ± 1.7		
Post Exercise	5.8 ± 1.3	6.2 ± 1.2	-0.02 (-8.2 – 0.4)	0.9
Change	0.2 (-0.8 – 0.4)	-0.3 (-0.01 – 0.7)		
***P*[b]**	0.5	0.06		
Cardiac Index (L/min/m^2)	n=15	n=16		
Baseline	3.1 ± 0.6	3.5 ± 0.7		
Post Exercise	3.2 ± 0.5	3.3 ± 0.5	-0.02 (-0.3 – 0.2)	0.9
Change	0.06 (-0.4 – 0.3)	-0.2 (-0.02 – 0.4)		
***P*[b]**	0.7	0.08		

Note: Unless otherwise stated data are given as mean and CI.

Abbreviations: AE, aerobic exercise; CE, combined exercise; CI, confidence interval; CO, cardiac output; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; TPR, total peripheral resistance; TPRI, total peripheral resistance index; SV, stroke volume.

[a]*P* values compare changes in the intervention and control groups and were estimated using regression models.

[b]*P* values test the within-group changes and were estimated using paired *t* tests or Wilcoxon signed-ranks test as appropriate.

Legends to Figures

Figure 1. CONSORT diagram to demonstrate flow of patients through the study.

Figure 2. Changes in knee extensor muscle strength. * denotes significant difference from baseline P<0.001; †denotes significant difference from baseline P<0.01; # denotes significant difference from change in AE group P<0.01.

Figure 3. Changes in quadriceps muscle volume. * denotes significant difference from baseline P<0.001; †denotes significant difference from baseline P<0.05. # denotes significant difference from change in AE group P<0.05.