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High intensity interval training in chronic kidney disease: a randomised pilot study

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ABSTRACT

Introduction. High intensity interval training (HIIT) increases mitochondrial biogenesis and cardiorespiratory fitness in chronic disease populations, however has not been studied in people with chronic kidney disease (CKD). The aim of this study was to compare the feasibility, safety and efficacy of HIIT with moderate intensity continuous training (MICT) in people with CKD. **Methods.** Fourteen individuals with stage 3-4 CKD were randomised to 3 supervised sessions/week for 12 weeks, of HIIT (n=9, 4x4 minute intervals, 80-95% peak heart rate [PHR]) or MICT (n=5, 40 minutes, 65% PHR). Feasibility was assessed via session attendance and adherence to the exercise intensity. Safety was examined by adverse event reporting. Efficacy was determined from changes in cardiorespiratory fitness (VO$_2$peak), exercise capacity (METs), and markers of mitochondrial biogenesis (PGC1α protein levels), muscle protein catabolism (MuRF1) and muscle protein synthesis (p-P70S6k ^{Thr389}). **Results.** Participants completed a similar number of sessions in each group, (HIIT=33.0[7.0] vs. MICT=33.5[3.3] sessions), and participants adhered to the target heart rates. There were no adverse events attributable to exercise training. There was a significant time effect for exercise capacity (HIIT=+0.8±1.2; MICT=+1.3±1.6 METs; p=0.01) and muscle protein synthesis (HIIT=+0.6±1.1; MICT=+1.4±1.7 a.u.; p=0.04). However, there were no significant (p>0.05) group x time effects for any outcomes. **Conclusion.** This pilot study demonstrated that HIIT is a feasible and safe option for people with CKD, and there were similar benefits of HIIT and MICT on exercise capacity and skeletal muscle protein synthesis. These data support a larger trial to further evaluate the effectiveness of HIIT.

The study was registered at the Australian and New Zealand Clinical Trials Registry-www.anzctr.org.au (Registration Number ACTRN12611001223921).

INTRODUCTION

Reduced cardiorespiratory fitness has been shown to be independently associated with a higher burden of cardiovascular risk in the chronic kidney disease (CKD) population (1). As such, exercise therapy in people with CKD improves cardiovascular disease risk factors, and may have an impact on health outcomes (2-4). However, there has been no work comparing the efficacy of different exercise prescriptions in this population. Moreover, it is unknown how exercise training may impact skeletal muscle oxidative capacity. High intensity interval training (HIIT) is superior to moderate intensity continuous training (MICT) in improving fitness and decreasing cardiovascular disease risk factors in both healthy and chronic disease populations (5-8). However, this type of training is yet to be evaluated in people with CKD.

In addition to cardiovascular benefits, exercise induced improvements in metabolic health can be attributed in part to increased skeletal muscle mitochondrial content (9). Improvements in mitochondrial biogenesis have been demonstrated to occur as a result of increased peroxisome proliferative activated receptor- γ coactivator-1 α (PGC-1α) activity after a single bout of low volume high intensity interval training (10). Studies by Tjonna et al. (2008) and Wisloff et al. (2007) identified significant increases in PGC1α (138% and 47% respectively), indicating enhanced mitochondrial biogenesis after HIIT, which was not found in the MICT group. This provides a plausible mechanistic link for the superior ability of HIIT to enhance cardiorespiratory fitness compared to moderate intensity exercise.

Muscle RING finger 1 (MuRF1), a marker of muscle atrophy, is a muscle specific E3 ubiquitin ligase that is increased in muscle atrophy conditions (11). This marker has been found to be elevated in rats with kidney injury (12). Further, people with chronic kidney disease have significant muscle wasting, with a study reporting 82% of CKD patients with strength below age-predicted normative

values (13). Aerobic training has been shown to reduce MuRF1 levels (ie. blocking the ubiquitin proteasome system activation) (14), however to our knowledge there has been no comparison of the effects of MICT and HIIT interventions on MuRF1. The increase in protein synthesis with aerobic training occurs through phosphorylation of the enzyme ribosomal protein S6 kinase (p70S6k), by activating the mammalian target of rapamycin (mTOR) signalling pathway (15). Further, it has previously been shown that in healthy males, HIIT is a stimulus for increased anabolic response by activating mTOR, leading to p70S6k activation (16).

To date, only one study has investigated the feasibility of higher intensity exercise in patients with CKD.(17) It was shown that patients with lower haemoglobin and exercise capacity, which are common with CKD, was a limiting factor in completing higher intensity exercise (not HIIT). HIIT has not been studied in CKD patients, and it is unknown whether the metabolic limitations associated with this disease would inhibit the ability to participate in this type of training. Further, patients with CKD have an increased cardiovascular burden, and so assessing the safety of exercising using this approach is pertinent.

Therefore, the aim of this pilot study was to investigate the feasibility, safety and efficacy of HIIT in people with CKD. It was hypothesised that HIIT would be feasible, with no untoward events occurring as a result of exercise training. It was also hypothesised that HIIT would elicit greater changes in cardiorespiratory fitness, exercise capacity, and markers of mitochondrial biogenesis, muscle protein catabolism and synthesis compared to MICT.

MATERIALS AND METHODS

Twenty-one individuals with stage 3-4 CKD (eGFR MDRD 25-60 ml/min/1.73m^2) were recruited for this pilot randomised control trial. Participants were invited to partake in this study after completion of the Landmark III trial (**L**ongitudinal **A**ssessment of **N**umerous **D**iscrete **M**odifications of **A**therosclerotic **R**isk in **K**idney disease), a 3-year randomised control trial lifestyle intervention (4). The study

protocol was approved by the Princess Alexandra (HREC/12/QPAH/456) and the University of Queensland (2011001397) Human Research Ethics Committees. All participants gave written, informed consent to participate in this study. The study was originally registered with ANZCTR to include three groups- a HIIT group, MICT group and a control (standard care) group. However, we had trouble recruiting patients with concerns that they would be randomised to the control group. Therefore, we changed the design to remove the control group. Further, the study was originally registered with ANZCTR to stratify by kidney function, but due to the limited range of kidney function in potential participants we removed this strata, and instead stratified by sex and diabetes status to ensure balanced groups. A technical error occurred in the VO_2peak post-test of one of the HIIT participants and as such there is only pre- and post-cardiorespiratory fitness data for eight HIIT participants. However, this participant had exercise capacity (METs) data. Two HIIT participants' muscle proteins did not extract well during Western Blot analysis and therefore were not included in the analysis. One HIIT participant did not undergo muscle biopsy as they were taking anti-coagulant medication. As such, muscle biopsy data was available for six HIIT participants and five MICT participants.

Randomisation was stratified by two levels- sex and diabetes status. Allocation was performed by an individual external to the study team and concealed to the study doctor who performed the muscle biopsy and supervised the exercise stress test. However, the primary researcher was not blinded due to limitations in resources. Participants were randomised in a 1:1 ratio into HIIT or MICT. Baseline demographics were attained from patient hospital files. Medication usage was reported by participants at the baseline visit.

Inclusion and exclusion criteria

Subjects with stage 3 or 4 CKD (modification of diet in renal disease [MDRD] eGFR 25-60 ml/min/1.73m^2) were included. Participants were aged 18 to 75 years and had at least one of the following risk factors at the time of enrolment – blood pressure or lipids not at target; overweight

(body mass index [BMI] >25 kg/m^2); and poor diabetic control (haemoglobin A1c >7%). Individuals were excluded if they had intervention for, or, symptomatic coronary artery disease (within 3 months), current heart failure (New York Heart Association class III and IV), significant valvular heart disease, Cardiologist deemed not suitable, pregnant or planning to become pregnant and life expectancy or anticipated time to dialysis or organ transplant <6 months. Specific to the current study, participants with an exercise stress test positive for ischaemia identified by their last Landmark III visit, or significant cardiac history, were assessed by their Cardiologist prior to enrolment. Participants with musculoskeletal disease that precluded high intensity exercise were also excluded.

Intervention

Participants undertook three sessions of exercise training per week for 12 weeks, supervised by an Accredited Exercise Physiologist (AEP). In line with reporting suggestions from the Consensus on Exercise Reporting Template (CERT) (18), the current study had a maximum practitioner to patient ratio of 2:1, with the AEP closely monitoring the intensity of each interval, rest period, and continuous training. The same AEP was present at all training sessions (with assistance from a research student) and had greater than 3 years' experience in chronic disease exercise prescription. The exercise intensity for each participant was individualised according to their peak heart rate (PHR) achieved in the initial cardiopulmonary exercise test. The work performed on the treadmill for the MICT group was isocalorically matched to the HIIT group, based on the American College of Sports Medicine's (ACSM) estimated energy expenditure calculations (19). Both HIIT and MICT groups performed a warm-up at 50-60% of PHR for five minutes and a cool down at the same intensity for three minutes. Table 1 shows the progression of target heart rates and interval times over the 12-week program, and how it compares to time spent training in the comparison MICT group. The high intensity group completed the HIIT 4x4 protocol that consisted of four intervals of four minutes duration, interspersed with 3 minutes of active recovery. The high intensity interval intensities were progressed between 80-95% of PHR over the 12 weeks, and the recovery intervals were set at 65% PHR. The PHR during the interval

was generally achieved in the final 2 minutes of the 4-minute interval, and the speed and incline of the treadmill was adjusted to maintain the target HR. The MICT group trained at an intensity of 65% PHR for 40 minutes per session. A treadmill was the primary modality of exercise; however, one participant completed the training on a cycle ergometer due to musculoskeletal limitations. The speed and incline of the treadmill/cycle ergometer were adjusted to ensure participants heart rate stayed at the desired intensity (within ~3 bpm). A chest heart rate (HR) monitor was used through the exercise session to assess training intensity in participants not on beta-blockers (n=10). Due to the effects of beta-blocker medication on HR, participants on beta-blockers (n=4) used BORG's rating of perceived exertion (RPE) scale to assess intensity rather than HR. The MICT group and the HIIT recovery interval were required to achieve an RPE of ~12-14, whereas the interval group were prescribed an RPE of 16-19 (20).

Feasibility

Feasibility was assessed via adherence to the exercise prescription. Adherence included both attendance to the prescribed sessions, and the ability to meet the intensity targets set in each session. Exercise enjoyment was assessed by the Physical Activity Enjoyment Scale (21). The seven-point Likert scale questionnaire was administered to participants in the week following completion of the 12-week intervention. The overall perceived exertion of the whole training session was measured by RPE on completion of each session, and the mean RPE across all sessions was calculated (22).

Safety

Participants were verbally asked to report any issues or problems which had occurred either during or following the exercise session. Adverse events were reported by research staff in an incident report form and were adjudicated by a medical doctor, to indicate whether they were attributable to

the exercise training. In line with research governance, any adverse events related to the study were also required to be reported to the ethics committee.

Efficacy

Efficacy measures were performed at baseline (prior to randomisation) and in the week after 12 weeks of training. Those participants taking beta-blocker medication were asked to abstain from taking the medication on the morning of testing.

Cardiorespiratory fitness, exercise capacity and physical activity

All participants completed the pre- and post-intervention cardiopulmonary exercise test on a treadmill. Cardiorespiratory fitness was assessed by measuring peak oxygen uptake (VO_2peak) using indirect calorimetry (Parvo Medics TrueOne 2400, UT, USA). The test protocol (Bruce, Balke or Naughton) was determined by the Duke Activity Status Index (23) and the same protocol was replicated post intervention. Exercise capacity (METs) was derived from the treadmill software based on the duration of the test (CASE V6.51, GE Medical Systems, Milwaukee, WI, USA). Participants were not allowed to use the hand rail, unless needed for balance. The self-reported Active Australia questionnaire was used to evaluate baseline average weekly physical activity levels (24). Total physical activity was calculated from the addition of walking, moderate intensity and vigorous intensity time in an average week in the preceding six-month period.

Muscle biopsy

Pre- and post- intervention muscle biopsies were performed 2 days after the exercise stress test, to avoid measurement of any acute responses to exercise. Muscle tissue was collected using the

suction-modified Bergstrom muscle biopsy technique (25) with a 5mm needle on the middle portion of the vastus lateralis, after administration of local anaesthesia (1% lignocaine). After extraction, muscle tissue was snap frozen in liquid nitrogen and stored at -80°C until subsequent analysis.

Western Blot Analysis

Skeletal muscle biopsy samples were homogenised, and SDS-PAGE performed as previously described (26). Membranes were probed with the following antibodies: anti-PPARγ coactivator-1α (PGC1α; Cell Signaling #2178), anti-muscle ring finger 1 (MuRF1; ECM Biosciences #MP3401), anti-P70S6K (Cell Signaling #2708) and anti-P70S6K p-Thr389 (Cell Signaling #9234).

Body composition

Dual energy x-ray absorptiometry (DEXA), using whole body composition analysis was used to determine body fat percentage and lean mass (Hologic QDR 4500A Version 12.6, Massachusetts, USA). Lower limb lean mass is reported as the sum of the lean mass in both legs.

Blood biochemistry and haemodynamics

Fasting blood samples were collected at baseline prior to any other testing. Serum vacutainers (BD vacutainers, Franklin Lakes, NJ, USA) were used to collect 10 ml venous blood samples following an overnight fast. Creatinine was measured by the Jaffe method on a Beckman DxC800 general chemistry analyser. eGFR was calculated by the Modification of Diet in Renal Disease (MDRD)-Creatinine equation (27). Resting blood pressure was taken in a seated position at the brachial artery after 5 minutes of quiet rest using a sphygmomanometer.

Statistics

Data were analysed via analysis of covariance (ANCOVA) to assess group x time interactions. The baseline value was entered as the covariate, and the change from pre-to post- intervention was used as the dependent variable. An independent samples t-test was used to compare between-group differences in variables which were only reported at 12 weeks. A Mann-Whitney U test was used for non-parametric variables. The analysis was a per-protocol analysis, as post-testing was not performed on participants who dropped out from the study. The main effect of time, and the interaction of group allocation and time, was assessed for each variable, with a p value of <0.05 considered statistically significant. Categorical variables were analysed using Pearson's Chi Square analysis. Data are presented as mean±SD. Non-normally distributed variable presented as median [IQR]. Categorical data are presented as n(%). All statistical analyses were performed on IBM SPSS Statistics 24.

RESULTS

Figure 1 outlines participant flow through the study; of the 50 eligible patients with CKD who were approached to participate but declined, nearly half (46%) cited a lack of time as a reason for not taking part. In total 21 participants were randomised to the study (Figure 1). Six of the nine participants in the HIIT group, and 3 of the five participants in the MICT group, were previously in the lifestyle intervention arm of the Landmark III study. The remaining five participants were from the control arm of Landmark III. Two participants from each group dropped out of the study, citing lack of time to participate in the intervention. Two participants from the MICT group dropped out of the study, due to a hip dislocation, and knee pain. One participant from the HIIT group dropped out of the study due to rheumatoid arthritis pain. These participants were not included in the final analysis.

Patient characteristics

Table 2 shows no significant baseline differences in patient characteristics between the HIIT and MICT groups. However, there were a greater number of participants in the MICT group on insulin. On average, participants had moderate (Stage 3) CKD with an eGFR of 34.3 ± 9.5 ml/min/1.73m^2 and were considered obese with an average BMI of 30.8 ± 5.6 kg/m^2. The HIIT group reported performing higher levels of physical activity (3.5[4.7] hours) per week at baseline, compared to the MICT group (1.5[4.0]), although this difference was not statistically significant.

Feasibility

Both groups completed a similar number of exercise sessions (Table 3). All participants in the HIIT and MICT group achieved their target heart rate or RPE for each interval.

Safety

There were no adverse events deemed attributable to the exercise training. Adverse events reported to the research team included a broken toe, hip dislocation, pain from knee arthritis, and a transient ischaemic attack.

Fitness measures

There were no between-group differences for any of the fitness measures over 12 weeks (Table 3). Figure 2 identifies the individual changes in exercise capacity and cardiorespiratory fitness.

Mitochondrial biogenesis

There were no significant group differences over 12 weeks for any of the skeletal muscle protein measures (Table 3). However, there was a trend for a time effect on PGC1α protein levels, with an increase of 14.3% for the HIIT group and 8.3% for the MICT group (Figure 2).

Muscle protein catabolism and synthesis

There was a trend for an increase in phosphorylation of P70S6k^{Thr389} over time, with an increase of 35% for the HIIT group and 45.2% for the MICT group. However, there were no group effects over time for total P70S6k or MuRF1 (Table 3).

Body composition and haemodynamics

There were no statistically significant changes in body composition or haemodynamics (Table 3).

Enjoyment and perceived exertion

There were no significant differences between the HIIT and MICT group for the physical activity enjoyment scale (Table 3). Participants in the HIIT group also reported non-statistically significant higher average RPE for the whole training session over the 12 weeks compared to the MICT group (Table 3).

DISCUSSION

This is the first study to investigate the effects of HIIT in people with CKD. The main findings are that HIIT is a feasible, safe and enjoyable exercise option for this population. However, in contrast to our hypothesis there was no added benefit of HIIT when compared to MICT for cardiorespiratory fitness and markers of skeletal muscle oxidative capacity or muscle protein catabolism or synthesis. Indeed, both HIIT and MICT significantly improved exercise capacity and protein synthesis.

Feasibility of HIIT

The findings from this small pilot study indicate that HIIT is a feasible training option for people with CKD. People with CKD have a high degree of co-morbidities and general lethargy, and whether this impedes the ability of these individuals to successfully complete HIIT has not previously been studied. It seems that the malaise experienced by people with CKD does not limit the ability to participate in HIIT (17). There was also no difference in enjoyment of exercise in the HIIT and MICT groups, which may have important implications for exercise adherence and long-term behaviour changes.

Safety of HIIT

The findings from this study indicate that HIIT is safe for people with CKD, with no adverse events occurring as a result of the exercise training. However, it is pertinent to note that HIIT still may only be appropriate for part of the population. As participants in this study had finished the Landmark III study, they had undergone thorough cardiac screening. They also underwent extensive blood work and review every 6 months. Moreover, in this 12-week study patients also completed an exercise stress test prior to randomisation. Thus, this was a highly screened group of CKD patients who may

not accurately reflect current patient populations. As a consequence of the screening, there were no underlying diseases detected that could be aggravated by high intensity exercise. In routine practice, exercise professionals working with people with CKD may not have access to this level of screening. Nevertheless, the risk of a cardiovascular event occurring was reported to be similar between HIIT and MICT in 4846 people with coronary heart disease (28). Therefore, we suggest that exercise physiologists should exhibit care when prescribing HIIT to CKD patients and seek medical guidance from treating physicians to determine the suitability of the patient before prescribing HIIT. Further studies are required to establish the safety of HIIT in a larger, more representative group of CKD patients.

Efficacy of HIIT

The findings from this pilot study indicate that HIIT induces similar benefits in exercise capacity as MICT. The increase in METs in both groups are clinically significant as it has been reported that for every 1 MET increase there is a 17% reduced risk of mortality (29). The observation that the MICT group had slightly greater improvements in exercise capacity and cardiorespiratory fitness was likely due to having considerably lower physical activity levels and fitness at baseline. This study did not show the same improvements in cardiorespiratory fitness as other cardiometabolic populations (6, 30). This could be due to a combination of the small sample size, heterogeneous nature of the CKD population or limitations in the capacity to increase physiological processes (eg. maximal stroke volume) that would improve VO_2peak. The ability to improve exercise capacity and not cardiorespiratory fitness is likely due to improved movement efficiency at submaximal workloads and is a reminder that these should be viewed as two different fitness measures.

Mitochondrial biogenesis is an essential process for maintaining skeletal muscle energy homeostasis and metabolism. The trend for greater improvements in PGC1α in the HIIT group is consistent with previous research suggesting that this type of training is superior for improving mitochondrial biogenesis in people with chronic diseases (31, 32). Indeed, Daussin et al. (2008) concluded that fluctuations in ATP turnover in interval training, which is different to usual steady state conditions of ATP production, activates the signalling pathways which leads to increases in PGC1α (33). Wisloff et al. (2007) found an increase in PGC1α to be strongly correlated with improved VO_2peak (r=0·72, p<0·01), supporting the influence of mitochondrial function on cardiorespiratory fitness (34). However, the increase in PGC1α in the current study was only 14.3%, as opposed to 47% in the study by Wisloff et al., which may explain the lack of improvement in VO_2peak in our findings.

The findings from our study indicate elevated basal post training phosphorylation of P70S6K[Thr389] in both MICT and HIIT groups, independent of any change in total P70S6K protein abundance. This suggests that both MICT and HIIT protocols elicit similar protein synthesis signalling responses that may have beneficial effects on skeletal muscle proteostasis in people with CKD. This is clinically significant, as skeletal muscle atrophy is associated with a three-fold increase in mortality in people with end stage renal disease (35).

Limitations

There are several limitations to this study. Firstly, our pilot study was based on a recruitment of 10 participants in each group, unfortunately we were unable to recruit this many participants. However, the lack of change in VO_2peak in the HIIT group, with an increase in METs was unexpected, and this non-response to physiological adaptation in this population warrants confirmation in a larger cohort. Moreover, the variability of VO_2peak in our cohort was significantly larger (SD 6.85) than the assumed VO_2peak variability previously reported in people with heart failure (SD 1.6) (31).

As such, to detect a significant difference in people with CKD, it is likely that sample size requirements are larger than other reported cardiometabolic populations. Secondly, although the baseline characteristics of this cohort were older adults, obese and appear to be typical of a CKD patient, the generalisability of the participants may be limited. Potentially, the individuals who volunteered to participate in a high intensity training study may be more motivated to make a significant lifestyle change. Indeed, the previous physical activity levels were high compared to the general population of the people with CKD from the Landmark III study at baseline. It would have been ideal to recruit participants with limited physical activity levels at baseline, however due to the difficulty in recruiting CKD participants for this trial, this approach would require a multi-centre approach with significant resources allocated to recruitment. Using heart rate monitors, the supervising exercise physiologist ensured that the HR reached the specific target zone for the session.[36] This was validated against RPE, and as such no changes to target HR through use of prediction equations was necessary. As recommended by our group [37], we ensured that the target heart rate was achieved by the first four minute interval, and then by approximately two minutes in the remaining intervals. RPE was used to guide intensity when there was an indication of inaccurate heart rate target zone.[37] Re-calibration using RPE was not necessary in the HIIT group (in the patients not on beta-blockers), but was required for some participants in the MICT group. In these instances, the RPE was reported lower than the percentage of MHR, (and therefore the workload was increased), likely due to the high resting HR in many patients with CKD.[38] Future large scales studies are also necessary to assess the optimal recovery time between HIIT sessions for older adults, and whether multiple HIIT sessions per week could be limiting improvements in cardiorespiratory fitness [39].

Conclusions

This pilot study identified that HIIT is feasible and safe for people with CKD. It also found that HIIT was as enjoyable as MICT despite a higher reported average session RPE. There were equal benefits of HIIT and MICT on exercise capacity and skeletal muscle protein responses. Based on these findings, both HIIT and MICT appear feasible options for people with CKD and exercise prescription should be based on patient history and interest.

PERSPECTIVE

The Norwegian 4x4 HIIT model, which has been well supported by the Scandinavian Journal of Medicine and Science in Sports, has proven to be efficacious in a number of clinical populations, providing an important contribution to exercise guidelines in higher risk patients. The findings from this paper is the first of its kind to evaluate HIIT in the chronic kidney disease population. This pilot study identifies that HIIT may be a safe inclusion in clinical care for patients with kidney disease. This is clinically important as people with chronic kidney disease are more likely to die from cardiovascular disease than progress to end-stage-renal failure. Chronic kidney disease also has a significant impact on quality of life, due to the high prevalence of sarcopenia. By identifying the potential role of HIIT and MICT in improving mitochondrial function, this study might identify a time efficient contribution to exercise training in kidney disease patients.

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Figure Legends

Fig. 1 Consort diagram

Fig. 2 Estimated METs, VO_2peak and PGC1α in each participant pre- and post-intervention

Table 1. Progression of target heart rates and interval times over the 12-week training period, with 3 supervised sessions/week. The total training time includes a five-minute warm-up and three-minute cool-down.

Weeks	Interval time (mins)	Interval intensity (% PHR)	Recovery time (mins)	Recovery intensity (% PHR)	HIIT total training time (mins)	MICT training time (mins)
1-2	4x3:00	80	3x2:00	65	26	30
3-4	4x3:00	85	3x2:00	65	26	31
5-6	4x3:00	90	3x2:00	65	26	38
7-8	4x4:00	90	3x3:00	65	33	40
9-12	4x4:00	95	3x3:00	65	33	40

PHR=peak heart rate; MICT=moderate intensity continuous training

Table 2. Patient characteristics

Variable	HIIT (n=9)	MICT (n=5)	p value
Age (years)	60.9±6.3	62.8±10.5	0.67
Female sex	3(33.3)	1(20)	0.60
eGFR (ml·min·1.73m^2)	33.8±10.8	34.8±8.2	0.86
Diabetes status	4(44.4)	4(80)	0.20
BMI (kg·m^2)	31.7±5.0	29.9±6.2	0.57
Previous PA levels (hours·week)	3.5[4.7]	1.5[4.0]	0.15
History			
Hyperlipidaemia	4(44.4)	4(80)	0.20
Myocardial infarction	1(11.1)	1(20)	0.65
Peripheral vascular disease	1(11.1)	0	0.44
Hypertension	9(100)	5(100)	
Stent	0	1(20)	0.16
Medication			
Ace-inhibitor	5(55.6)	4(80)	0.36
β-blocker	2(22.2)	2(40)	0.48
Thiazide	1(11.1)	1(20)	0.65
Statin	5(55.6)	3(60)	0.87
Insulin	0	3(60)	**<0.01**
Allopurinol	4(44.4)	0	0.08

PA= physical activity. Data are presented as mean±SD. Not normally distributed variable presented as median [IQR]. Categorical data is presented as n(%)

Table 3. Baseline and 12-week changes in primary and secondary outcome measures

Variable	MICT Baseline	Change	HIIT Baseline	Change	p value	Partial eta^2	95% CI
Systolic blood pressure (mmHg)	137.5±16.4	-9.8±11.1	129.3±12.22	+1.3±15.3	0.09	0.28	[-2.39, 25.1]
Diastolic blood pressure (mmHg)	77.0±8.1	-11.0±9.4	77.6±13.2	+4.3±12.8	0.12	0.25	[-4.17, 31.82]
Fitness measures							
METs	9.8±3.4	+1.3±1.6	8.8±3.4	+0.8±1.2	0.63	0.02	[-1.99, 1.26]
VO$_2$peak (ml·kg·min)	22.3±7.6	+1.6±2.3	21.7±6.1	+0.1±2.4	0.34	0.09	[-4.46, 1.68]
VO$_2$peak (L·min)	2.0±0.6	+0.1±0.1	1.8±0.4	0.0±0.3	0.93	<0.01	[-0.35, 0.32]
Respiratory quotient	1.1±0.1	0.0±0.1	1.1±0.1	0.0±0.1	0.26	0.13	[-0.05, 0.16]
Anthropometry							
Weight (kg)	86.2±9.6	-1.3±1.9	84.9±25.3	+0.1±2.0	0.21	0.14	[-0.96, 3.91]
Body fat (%)	37.7±8.2	+0.2±2.8	35.1±5.6	+0.1±1.5	0.91	<0.01	[-2.79, 2.50]
Lower limb lean mass (kg)	17.0±2.8	+0.3±2.4	17.6±6.6	-0.4±1.2	0.50	0.05	[-2.87, 1.52]
Muscle biopsy data							
PGC1α (a·u)	1.2±0.3	+0.1±0.3	1.1±0.2	+0.2±0.2	0.61	0.04	[-0.30, 0.48]
MuRF1 (a·u)	1.0±0.2	+0.1±0.2	0.9±0.2	0.0±0.3	0.69	0.02	[-0.52, 0.36]
P70S6k (a·u)	1.2±0.2	0.0±0.3	1.0±0.1	-0.1±0.1	0.80	0.01	[-0.37, 0.29]
p-P70S6k^{Thr389} (a·u)	1.8±1.1	+1.4±1.7	1.7±0.7	+0.6±1.1	0.38	0.10	[-2.85, 1.23]
Attendance, enjoyment and exertion	**12 weeks**		**12 weeks**	**Group**			
Sessions attended	33.0[7.0]		33.5[3.3]	0.30			[-5.33, 0.83]
Physical activity enjoyment scale	71±10.0		63.5±21.4	0.20			[-4.31, 19.31]
Session rating of perceived exertion	14.6±2.4		13.5±2.0	0.29			[-1.10, 3.41]

Change data is reported as 12 week minus baseline values. CI = confidence interval [lower limit, upper limit].

Eligible participants approached
from the Landmark III study
(n=71)

Underwent baseline testing
and randomisation (n=21)

HIIT
(n=12)

MICT
(n=9)

Lost to follow up
(n=3)
Withdrew- citing
lack of time: n=2
Health reasons-
rheumatoid
arthritis pain: n=1

Lost to follow up
(n=4)
Withdrew- citing lack
of time: n=2
Health reasons- hip
dislocation, knee pain:
n=2

HIIT
(n=9)

MICT
(n=5)

HIIT
MICT