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Intradialytic exercise as anabolic therapy in haemodialysis patients – a pilot study

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Summary

Haemodialysis (HD) patients are characterized by muscle wasting and consequently decreased physical functioning and poor outcome. This pilot study investigated if a novel intradialytic exercise programme could increase lean mass via up-regulation of the insulin-like growth factor (IGF) system. Nine HD patients were assessed before (w-12) and after a 3-month control phase (w0), after a three-month intradialytic interval training programme using high intensity cycle exercise (w12), and after a withdrawal of treatment phase (w24). Body composition was determined by dual energy X-ray absorptiometry (DEXA) and bioelectrical impedance spectroscopy (BIS); physical functioning by knee extensor strength (KES) and 30-s sit stand test (SST); and IGF-I and IGFBP-3 in serum and muscle by radioimmunoassay. Despite significant increases in training load (+274%, $P<0{\cdot}001$), peak power output (+71%, $P<0{\cdot}001$) and physical function (KES: +19%, $P<0{\cdot}05$; SST: +20%, $P<0{\cdot}05$) following the intervention phase, lean masses by DEXA, intra cellular water by BIS (a surrogate measure of body cell mass) and serum and muscle IGFs remained unchanged following training. Although this novel exercise programme, utilizing high intensity interval training, was safe, clinically feasible and beneficial in terms of physical functioning, the 12 weeks of intradialytic cycle exercise failed to reverse the muscle atrophy characteristic of this population. Future studies, using primary outcome measures similar to those employed in the present study, should investigate other anabolic interventions to determine potential treatments for the muscle wasting associated with end stage renal disease.

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Introduction

Patients with end stage renal disease (ESRD) have reduced skeletal muscle mass (Woodrow *et al.*, 1996) that is associated with poor physical function (Johansen *et al.*, 2003) and increased mortality (Beddhu *et al.*, 2003). Hence interventions that increase muscle mass in ESRD patients have the potential to improve patient outcome in this population.

Exercise training has been successfully used to treat muscle wasting in other catabolic diseases (Zinna & Yarasheski, 2003). Although progressive resistance training (PRT) is likely to be the most anabolic of exercise interventions in ESRD (Castaneda *et al.*, 1998), PRT programmes are difficult to implement during dialysis sessions, recommended as an optimal time to perform exercise because of increased programme compliance (Konstantinidou *et al.*, 2002). Interestingly, reduced muscle protein catabolism (Davis *et al.*, 1983), increased mean muscle fibre cross sectional area (Kouidi *et al.*, 1998; Sakkas *et al.*, 2003) and improved nutritional assessment scores (Mercer *et al.*, 2004) have been observed following predominantly aerobic exercise interventions in uraemia. These findings are of importance because aerobic training programmes can be implemented during dialysis sessions. However, these observations have not been confirmed using a direct assessment of body composition, which is the primary outcome measure to determine the effectiveness of anabolic interventions in muscle wasted populations (Senior & Maroni, 1999).

Consequently, with a view to implement a larger, randomized, controlled trial, the aim of this pilot study was to assess the feasibility and safety of a novel, high intensity, interval, intradialytic, cycle exercise programme and to quantify its effect on body composition and physical functioning. A secondary aim of this study was to assess the effects of the exercise programme on one step of the signalling cascade that is responsible for

muscle hypertrophy, the muscle insulin-like growth factor (IGF) system, which is known to be altered in ESRD (Ding *et al.*, 1996; Macdonald *et al.*, 2004).

Methods

Subjects and design

Haemodialysis (HD) patients were recruited from Gwynedd District General Hospital renal unit. Exclusion criteria were unstable medical condition (angina, uncontrolled hypertension, congestive heart failure, and cardiac arrhythmias), use of corticosteroids, anabolic therapies or participation in exercise programmes within the last 6 months, comorbid catabolic conditions, diabetes mellitus, hyperparathyroidism, vasculitis and known neuro-muscular disorders. Of the 64 patients in the renal unit, 18 patients met the inclusion criteria and 10 volunteered to take part. Clinical and demographic data is shown in Table 1. All subjects were receiving medications for blood pressure control and erythropoietin therapy to maintain haemoglobin above 10 dl^{-1}. Ethical approval was obtained from the North West Wales Local Research Ethics Committee and all participants gave written informed consent. This pilot study utilised a repeated measures design (Fig. 1).

Exercise intervention

Although PRT is the most anabolic of exercise interventions, it can rarely be performed during dialysis because of space and staff restrictions on renal units. A high intensity interval-training programme was therefore chosen to provide maximum possible muscle overload whilst remaining clinically applicable. Although the anabolic nature of this type of programme is unclear, theoretically it may be more anabolic than continuous aerobic exercise as a greater intensity (power output) and greater training load (total work done) is achievable (Puhan *et al.*, 2004), promoting muscle overload (Kraemer *et al.*, 2002).

Table 1 Demographic and clinical data of study subjects.

Number (males/females)	9 (7/2)
Age (years)	48·4 ± 5·3
Height (cm)	170·4 ± 3·1
Body mass index (kg m^{2-1})	24·8 ± 1·5
Dialysis prescription (h)	3·8 ± 0·2 thrice weekly
Time on dialysis (months)	26·7 ± 5·9
Haemoglobin (g dl^{-1})	11·7 ± 0·4
nPNA (g kg^{-1} day^{-1})	1·2 ± 0·1
Albumin (g l)	41·3 ± 1·8
HCO_3^- (mmol l)	27·6 ± 1·1
Pth	13·1 ± 3·9
K_t/V_{urea}	1·4 ± 0·1

nPNA, normalized protein nitrogen appearance(an indirect indicator of protein intake); HCO_3^-, serum bicarbonate (an indirect marker of acidosis); Pth, parathyroid hormone; K_t/V_{urea}, a measure of dialysis adequacy. Data are means ± SE.

Patients completed 12 weeks of thrice weekly interval-training of the lower legs performed on adapted cycle ergometers (Rehab 881/E, Monark, Sweden) under supervision of an exercise physiologist. During the first hour of the dialysis session, whilst in a semi recombinant position, patients exercised at high intensity for 2-min bouts, each separated by 2 min of active recovery (see below for details), and worked towards completing 15 bouts per session. Total work done (workload in watts multiplied by number of cycle revolutions) and peak power output (highest power output sustained for a complete bout) were recorded each session. Patients who missed more than 1 week of exercise resumed their programme once they had regained their previous fitness level, and all patients completed a minimum of 36 sessions.

Because of the variability of heart rate and blood pressure during haemodialysis, the 6–20 rating of perceived exertion scale (RPE) was used as the primary method of controlling intensity. Subjects were blinded from their power output so that it could not influence their RPE assessment. Intensities of RPE 9 (assumed to equate to 50% $\dot{V}O_{2max}$) were used for warm up and cool down, RPE > 17 (~90% of $\dot{V}O_{2max}$) for training intervals and RPE 7 (<40% $\dot{V}O_{2max}$) for active recovery (Williams & Eston, 1989). Training load (i.e. power output) was increased during the study to account for improving fitness by patients selecting a higher power output for the requested RPE.

Primary outcome measures

Regional and whole body lean mass, fat mass and bone mineral content were assessed by dual energy X-ray absorptiometry (DEXA, QDR1500, software version 5·72; Hologic, Waltham, MA, USA). Intra (ICW) and extra (ECW) cellular water were assessed by bioelectrical impedance spectroscopy (BIS, Hydra ECF/ICF 4200; Xitron Technologies, San Diego, CA, USA).

Secondary outcome measures

Lower body physical functioning was quantified by knee extensor static strength (KES) assessed by a handheld dynamometer (CSD 300; Chatillon, Largo, FL, USA) and 30-s sit to stand test (SST) performance (Macdonald *et al.*, 2004).

Other measures

Height was determined using a wall-mounted stadiometer (Body Care, Warwickshire, UK). Serum ($n = 9$ at all assessment time points) and muscle ($n = 5$ at weeks − 1 and 13 only) samples were collected, prepared and analysed as previously described (Macdonald *et al.*, 2004). Briefly, serum and muscle IGF-I (sIGF-I and mIGF-I) and IGF binding protein-3 (sIGFBP-3 and mIGFBP-3) concentrations were measured by in-house specific radioimmunoassays. For the IGF-I assays, endogenous binding proteins were first removed using an acid/acetone extraction procedure and saturation in excess IGF-II. The

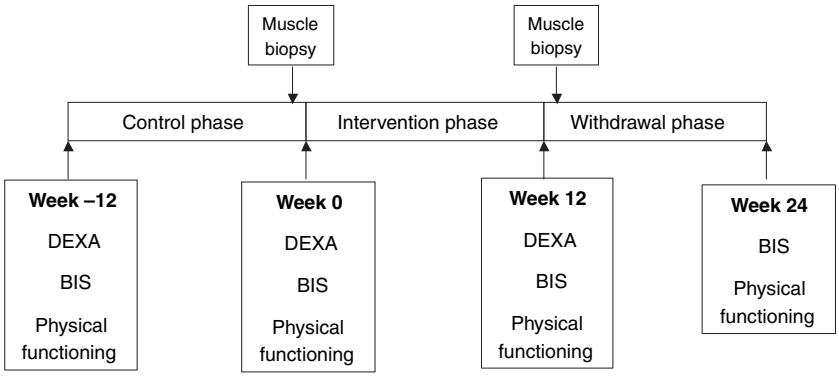

Figure 1 Study design and timing of outcome measures. DEXA, dual energy X-ray absorptiometry; BIS, bioelectrical impedance spectroscopy.

intra- and interassay coefficient of variations (CVs) were 3 and 15%, respectively for IGF-I, and 4 and 14%, respectively for IGFBP-3. Fragmentation of systemic IGFBP-3 was determined by Western immunoblotting.

Statistical analysis

Differences between means were analysed by one way repeated measures analysis of variance (RM ANOVA) with Tukey's Honestly Significant Difference *post hoc* tests. In addition, as advocated by Koufaki *et al.* (2002b), to aid in the interpretation of statistical hypothesis testing in this heterogeneous population, variability of our main outcome measures was assessed by calculating CV and standard error of the measurement (SEM) between week −12 and week 0 (the same duration as our intervention). Linear regression analysis (Pearson's r) was used to analyse associations between variables. The level of statistical significance was set as $P<0{\cdot}05$, and all analyses were performed on a statistical computer package (SPSS version 11; SPSS, Chicago, IL, USA). Values are expressed as mean ± SE.

Results

Exercise intervention

Ten subjects were originally recruited into the study. One patient dropped out because of back pain when cycling, a condition caused by previously collapsed vertebrae. The exercise programme was well tolerated in the other nine subjects who completed the requirements of the training and testing protocol. Total work done per session (w0 = 2336·7 ± 548·6, w12 = 8728·9 ± 1571·0 kilopond metres, $P<0{\cdot}001$), and peak power output (w0 = 38·3 ± 7·4, w12 = 65·6 ± 8·9 watts, $P<0{\cdot}001$) significantly improved during the training period, and by week 12 all but one patient could complete at least 13 bouts per session.

Primary outcome measures

Body composition data appears in Table 2. All variables determined by DEXA remained unchanged during the control phases and following 12 weeks of high intensity cycling, so to avoid unnecessary X-ray exposure subjects were not re-measured following the withdrawal phase. The CV for total lean mass was 2·4%, and the SEM was 1·14 kg. Following exercise training, ICW, a proxy measure of body cell mass, also remained unchanged. In contrast, ECW significantly decreased 6·7% following the 12-week training period before returning to control values during the withdrawal phase. Individual patient assessment revealed that seven patients decreased their ECW by more than 1 SEM. The CVs for ICW and ECW measures were 7·4 and 4·1%, respectively and the SEMs 1·33 and 0·55 l, respectively.

Secondary outcome measures

Although no increases in lean mass were observed in response to the exercise intervention, RM ANOVA revealed a significant main effect of time for SST (Fig. 2) and KES (w-12 = 22·5 ± 2·9, w0 = 23·5 ± 4·2, w12 = 28·0 ± 4·0, w24 = 24·8 ± 4·4 N, $P<0{\cdot}05$). *Post hoc* comparisons revealed both lower body measures of physical functioning significantly increased ∼20% following the training period before returning towards (for SST data) or completely attaining (for KES data) control values during the withdrawal phase. Individual patient assessment revealed eight patients improved both physical functioning measures by more than 1 SEM. The CVs for SST and KES were 5·5 and 14·4% respectively, and the SEMs 0·47 reps and 3·04 N, respectively. Positive correlations between lean masses and lower body physical functioning strengthened following exercise training (leg lean mass and KES, at week −12, $r = 0{\cdot}636$, $P<0{\cdot}05$; at week 12, $r = 0{\cdot}771$, $P<0{\cdot}01$).

Other measures

No changes in sIGF-I, sIGFBP-3 or sIGFBP-3 fragmentation were observed following the exercise intervention (data not shown). While mean mIGF-I increased 57% (normalized to total protein: w0 = 0·94 ± 0·31, w12 = 1·48 ± 0·23 pg μg^{-1}), this response was variable amongst the subjects and did not attain significance ($P=0{\cdot}237$ by t-test). No response to the exercise intervention was evident for mIGFBP-3 (normalised to total protein: w0 = 9·47 ± 2·25, w12 = 7·93 ± 1·86 pg μg^{-1}, $P=0{\cdot}698$ by t-test).

Blood pressure medication use dropped significantly, with the number of medications decreasing by 30% during the

	Control 1 (week–12)	Control 2 (week 0)	Post intervention (week 12)	Withdrawal (week 24)	*P*-value
Weight (kg)	70·6 ± 4·7	70·9 ± 4·8	71·0 ± 5·0	–	0·860
Fat mass (kg)	20·0 ± 3·8	20·3 ± 3·7	20·8 ± 3·7	–	0·504
BMC (kg)	2·4 ± 0·2	2·4 ± 0·2	2·4 ± 0·1	–	0·494
Lean mass (kg)	48·2 ± 3·0	48·3 ± 3·0	47·8 ± 3·2	–	0·536
Trunk lean mass (kg)	25·6 ± 1·5	25·6 ± 1·2	25·1 ± 1·6	–	0·318
Leg lean mass (kg)	14·1 ± 1·0	13·9 ± 1·0	13·9 ± 1·1	–	0·879
Arm lean mass (kg)	5·0 ± 0·5	5·1 ± 0·5	5·0 ± 0·5	–	0·358
ICW (L)	20·2 ± 1·9	19·9 ± 1·9	19·7 ± 1·7	20·0 ± 1·8	0·858
ECW (L)	16·2 ± 1·3	16·4 ± 1·0	15·3 ± 1·2*	16·2 ± 1·1	<0·05

Table 2 Body composition data by dual energy X-ray absorptiometry (DEXA) and bioelectrical impedance spectroscopy of nine haemodialysis patients.

Data are mean ± SE. P-values are for RM ANOVA.
BMC, bone mineral content; weight, sum of fat mass, BMC and lean mass by DEXA.
*Intervention phase significantly different from control and withdrawal phases by Tukey *post hoc* test.

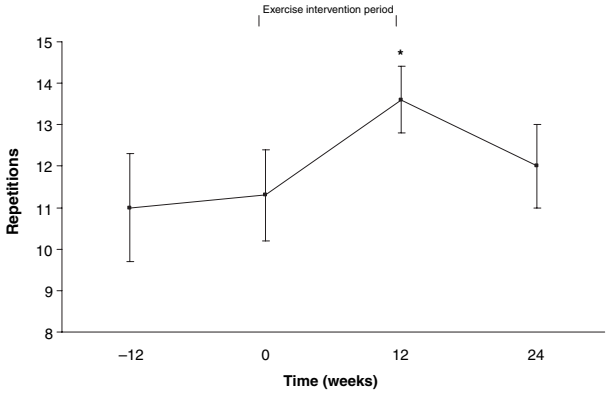

Figure 2 Maximum number of sit to stand repetitions in 30 s. *P<0·05 from control phases by RM ANOVA and Tukey *post hoc* test. Data are mean ± SE.

intervention period (P<0·05). Despite this reduction and stable diastolic blood pressure (P=0·725), monthly mean predialysis systolic blood pressure (sBP) decreased significantly during the intervention phase (−5·4%, P<0·05). Number of medications and sBP returned towards baseline levels following the withdrawal phase.

Discussion

The aim of this pilot study was to assess the feasibility and safety of a high intensity interval cycle exercise programme in patients with ESRD, and to assess its effect on lean masses and physical functioning. To the best of our knowledge no previous study in ESRD has utilized this type of exercise intervention or evaluated whether exercise in general can reverse muscle atrophy using recommended body composition techniques (Senior & Maroni, 1999).

Despite being very high intensity, the novel exercise intervention was well tolerated and safe in this population. The exercise programme was performed during dialysis, which is known to increase programme compliance (Konstantinidou *et al.*, 2002). Furthermore, patients were able to continue to exercise in a similar manner without exercise physiologist supervision when the research study stopped. Taken together, these findings suggesting the programme is clinically feasible in this population and could be run in renal units by nursing staff.

In terms of effect, the exercise programme successfully improved markers of lower body physical functioning, as both KES and SST performance increased during the intervention phases to a greater degree than the variability of these measures. A novel finding was that KES and SST data returned towards control phase values upon withdrawal of treatment, suggesting that, as for healthy individuals, continued training is required to maintain exercise-induced improvements. Our results also tentatively suggest that an interval method of training does not offer obvious advantages over the more traditional continuous aerobic exercise programmes used in other studies, as the improvements we observed in physical functioning of about 20% are similar to those previously reported (Cappy *et al.*, 1999; Painter *et al.*, 2000; Koufaki *et al.*, 2002a).

However, despite evidence of a significant training effect, the interval exercise programme failed to elicit an anabolic response as evidenced by stable whole body and lower body lean mass by DEXA, intra cellular water by BIS, and analysis of IGF-I and IGFBP-3 in serum and muscle. As no anabolic effect was observed, alterations in functional capacity after 3 months of interval cycle training must be due to other adaptations, such as cardiac alterations, peripheral changes such as enhanced muscle oxygen uptake and/or improved neural function (Kouidi, 2001). Interestingly, in our study the correlations between lean mass and functional capacity increased following training, suggestive of a shift towards a normal muscle volume/muscle strength relationship. This explanation is in agreement with other authors who have noted improved muscle morphology in uraemic patients following training (Kouidi *et al.*, 1998; Sakkas *et al.*, 2003).

One possible explanation for the lack of an anabolic response is that the exercise programme failed to provide sufficient training load. Indeed, previous studies that have suggested aerobic exercise may have anabolic effects in uraemia were of

longer duration. For example, Kouidi *et al.* (1998) provided, in total, 60 h of training time over a 6-month period, Sakkas *et al.* (2003) provided 48 h over a 6-month period and Davis *et al.* (1983) provided 40 h over a 5-week period, and each training protocol successfully increased muscle fibre cross sectional area. The present study provided only 36 h of training over a 3-month period, half of which would have been performing active recovery and thus providing minimal load, and no increase in lean masses were observed. Thus despite the higher intensity utilized with the present protocol, total work done may have been greater in the previous studies. To enable design of the most efficient training protocols, these indirect comparisons require confirmation by further prospective studies to determine the relative importance of factors such as mode, intensity and duration on anabolic response in ESRD. Furthermore, these studies should include recommended outcome measures, which determine lean mass, skeletal muscle mass, body cell mass or total body protein, to assess the effectiveness of these potential anabolic interventions (Senior & Maroni, 1999).

A surprising finding from the present study was that exercise training significantly decreased ECW, possibly due to exercise induced sweating in the warm environment of the dialysis ward. Although a decrease in ECW with a stable lean mass by DEXA could be indicative of a body protein increase and thus be interpreted as an anabolic response, ICW [a proxy measure of body cell mass, (Earthman *et al.*, 2000)], calculated body cell mass using models suggested by St Onge *et al.* (2004) (data not shown), and muscle IGF-I [one of the anabolic hormones in the signalling cascade required to trigger muscle hypertrophy (Adams, 2002)] did not significantly change during the study period. Concurrent with this decrease in ECW was a significant decrease in blood pressure medication with no resultant increase in blood pressure. As it is well documented that cardiovascular disease caused by increased ECW is a major cause of mortality in HD patients (Charra & Chazot, 2003) investigating whether these findings are linked warrants further investigation.

In conclusion, this is the first study to utilize an interval exercise programme in ESRD, and to assess its effectiveness using primary outcome measures for anabolic interventions. Although the exercise programme was of high intensity, it was feasible and safe in this population. Similar to previous exercise studies in ESRD, physical functioning was markedly improved following the exercise intervention. However, the 12-week protocol failed to increase lean mass as measured by our methods. Future studies, using outcome measures such as those presented here, should research other anabolic interventions to determine clinically practical treatments for muscle atrophy in ESRD.

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