Progressive resistance training during hemodialysis: Rationale and method of a randomized-controlled trial

Birinder S. B. CHEEMA,1 Anthony J. O’SULLIVAN,2 Maria CHAN,3 Aditi PATWARDHAN,4 John KELLY,5 Adrian GILLIN,6 Maria A. FIATARONE SINGH7,8

1Institute of Food, Nutrition and Human Health, Massey University, Wellington, New Zealand and School of Exercise and Sport Science, University of Sydney, Sydney, Australia; 2Department of Medicine, University of New South Wales, Sydney, Australia; 3Department of Nutrition and Dietetics and St. George Hospital, Sydney, Australia; 4Department of Nutrition and Dietetics and Royal Prince Alfred Hospital, Sydney, Australia; 5Department of Renal Medicine, St. George Hospital, Sydney, Australia; 6Department of Renal Medicine, Royal Prince Alfred Hospital, Sydney, Australia; 7Faculty of Medicine and School of Exercise and Sport Science, University of Sydney, Sydney, Australia; 8Hebrew Senior Life and Jean Mayer USDA Human Nutrition Center on Aging at Tufts University, Boston, Massachusetts, U.S.A.

Abstract
Skeletal muscle wasting in patients receiving maintenance hemodialysis (HD) has been well documented. The rationale for prescribing progressive resistance training (PRT) in this cohort in an attempt to reverse this catabolism and induce a wide spectrum of physiological, functional, and psychological health-related adaptations is extremely strong. Unfortunately, the barriers to exercise adoption in this cohort are many, which may explain the persisting sedentariness of this population and the lack of widespread clinical programs such as are now commonplace in cardiac rehabilitation and pulmonary rehabilitation units. Current health care practices for HD patients do not address the negative health issues of inactivity and muscle wasting. Therefore, we conducted the first randomized-controlled trial to prescribe PRT during maintenance HD treatment. The purpose of this paper is to present the rationale and methodology that we utilized for implementing intradialytic PRT in a conventional outpatient HD clinic. Potential areas for modification of PRT regimens in this setting are also presented.

Key words: End-stage renal disease, muscle, clinical practice, exercise, sarcopenia

INTRODUCTION

A rationale for resistance training during Hemodialysis (HD)

According to the United States Renal Data System, the incidence and prevalence of end-stage renal disease (ESRD) continues to rise each year. Over 102,000 new cases were reported in the USRDS 2005 report, and over 93,000 of these individuals commenced maintenance HD treatment as renal replacement therapy. Currently, over 300,000 patients in the United States receive HD. With continued growth of this patient population expected in the years ahead, greater efforts must be directed toward improving the long-term survival and quality of life (QOL) of this vulnerable cohort. Among chronic illnesses, ESRD is prominently associated with skeletal muscle wasting. Catabolism, with its intimate relation to the malnutrition-inflammatory complex, is the most significant predictor of mortality in
this cohort. The structural abnormalities of skeletal muscle at the cellular and subcellular levels have been well described. Concomitant metabolic changes include decrements in protein synthesis, and glucose and lipid metabolism, influenced to a large extent by a catabolic milieu (i.e., hormones and cytokines), insulin resistance, and mitochondrial dysfunction.

Metabolic abnormalities resulting from skeletal muscle wasting can also increase visceral obesity, which elevates the risk of cardiovascular disease, the leading cause of death in patients with ESRD. The functional consequences of catabolism include weakness, fatigue, reduced ability to generate force, reduced exercise tolerance, and impaired performance of daily activities, all of which are highly prevalent complaints among HD patients. Overall, muscle catabolism in ESRD is associated with increased morbidity and mortality, depression, and significantly reduced QOL.

The etiology of skeletal muscle wasting in HD patients has not been completely defined. Acidosis, oxidative stress, hyperparathyroidism, neuropathy, protein-restricted diets, anorexia, cytokines, HD treatment, and other factors appear to be involved. Lifestyle restrictions, including the inactivity imposed by 12 to 18 hr weekly of dialysis treatment, may also contribute markedly to this degenerative process. Prevalent psychological impairments such as depression and anxiety may negatively impact upon lifestyle choices regarding optimal diet and exercise, which may further compound the catabolic cascade. Hemodialysis patients are significantly less active than healthy, sedentary individuals, and a low intrinsic motivation has been identified as a major barrier to prescribing exercise in this cohort.

To foster exercise adoption in this cohort, several investigators have prescribed exercise during HD treatment. Studies evaluating the efficacy of intra-dialytic exercise training to date have utilized cycle ergometer training as the major, or sole component of the exercise regimen. These trials have demonstrated that exercise during dialysis can induce significant physiological, functional, and psychological benefits, is feasible to administer, has important clinical relevance, and results in no serious adverse events. However, while cycle ergometer training appears to be safe and effective when performed during dialysis, such a conditioning is not the preferred modality for reversing muscle catabolism.

Progressive resistance training (PRT) by contrast has become well established as the modality of choice for inducing skeletal muscle hypertrophy in healthy adults and those with frailty and/or chronic disease. Unfortunately, there has been very little exploration of the myogenic, and overall health-related impact of PRT in HD patients to date. Kouidi et al., in an uncontrolled trial involving 7 HD patients, reported that an exercise program performed on nondialysis days resulted in Type 1 and Type 2 muscle fiber hypertrophy (29%) with a normalization of skeletal muscle morphology at the cellular and subcellular level. However, the multi-modal exercise intervention implemented in this study, involving both aerobic and low-intensity strength training, precludes assigning the beneficial changes specifically to the use of strengthening exercise. To date, Headley et al. have conducted the only trial prescribing isolated PRT in ESRD. This study did not evaluate muscular adaptations, however. Moreover, similar to Kouidi et al., the intervention was performed on nondialysis days, few patients (N=10) were enrolled, and there was no control group.

The rationale for prescribing PRT to HD patients is extremely strong, given the elevated risk of myopathy. However, the barriers to exercise adherence in this cohort are many. Access solely to sedentary pursuits, such as reading and watching television, are currently the only leisure-time pursuits available to patients in most dialysis units. This continually reinforced sedentary behavior coupled with abnormally low occupational and recreational activity likely exacerbates muscle catabolism and the concomitant decline of overall health status in this cohort. Moreover, it has become evident that there are almost no routine rehabilitation programs for HD patients such as are now commonplace in cardiac rehabilitation and pulmonary rehabilitation units, and exercise counseling practices among nephrologists remain low.

At present, there is a vital need to integrate the basic tenets of exercise prescription with those of mainstream medical practice in an attempt to improve the health status and QOL of this vulnerable patient population. Accordingly, our research group, comprised of exercise physiologists, physicians, nephrologists, and renal dietitians, postulated that full-body PRT could be carried out during routine, outpatient HD treatment sessions. Such an approach creatively modifies the dialysis care setting and may influence patients to assume greater control over their illness and lives. Intradialytic PRT may be easily supervised, may maximize adherence and progression, requires no additional time commitment by the patients, may relieve the boredom and anxiety associated with dialysis sessions, and may facilitate behavior change by constant patient role modeling. In our current randomized-controlled trial we hypothesized that our PRT regimen would be feasible to administer, safe to perform,
and beneficial with respect to inducing muscle hypertrophy and associated health-related adaptations in our patients. Our methodology for applying PRT in this novel setting is described in detail herein, to facilitate replication and improvement of this intervention within dialysis care settings and future clinical trials.

A METHOD FOR INTRADIALYTIC RESISTANCE TRAINING

Setting and study design
The present clinical trial was conducted at the outpatient HD unit of the St. George Public Hospital, Sydney, Australia. Ethics approval was obtained from the South Eastern Sydney Area Health Service and the University of Sydney Ethics Committees. The initial phase of the study involved a randomized-controlled trial comparing patients receiving usual care HD treatment (wait-list control group), with patients receiving usual care HD treatment plus PRT (exercise group) for 12 weeks. Following this initial phase of the study, subjects randomly assigned to the control group performed PRT for 12 weeks, while the E group continued to perform PRT for an additional 12 weeks (24 weeks total). This crossover study design was utilized for ethical reasons, given that all PRT sessions performed by the exercise group during the initial 12 weeks of the trial were performed in the presence of those subjects randomly assigned to the wait-list control group.

The medical screening process
Patients were approached for participation in the trial if all of the following criteria were met: (1) age $\geq 18$, (2) basic comprehension and communication of English, (3) maintenance HD treatment received for ESRD for $\geq 3$ months, (4) adequately dialyzed ($\text{Kt/V} \geq 1.2$) and stable on HD, (5) expected to remain on HD treatment for at least 6 months, (6) ambulatory with or without an assistive device but without direct assistance of a person for at least 50 m, and (7) no acute or chronic medical conditions that would make PRT potentially hazardous or primary outcomes impossible to assess.

Given that patients of various ages, fitness levels, comorbidities, and stability on dialysis were likely to be encountered, a staged medical screening process to determine patient eligibility was warranted. The medical screening process involved the following: (1) review of the medical record and clinical HD notes of the patient by the on-site exercise physiologist, (2) review of that information by the principal investigator (M.A.F.S.), (3) interview of the patient by the on-site exercise physiologist, (4) consent of the nephrologist of the patient via medical screening checklist, and (5) physical examination and interview by a study physician (A.J.O). The purpose of the examination was to determine the level of stability of the patient during HD, and to detect any signs or symptoms indicative of a possible contraindication to intradialytic PRT.

If no potential contraindications were evaluated and the patient was deemed “stable on dialysis,” the patient was approached for their consent to participate in the trial. Approximately 18.3% (26/142) of patients screened were excluded from the training program owing to medical reasons listed.

<table>
<thead>
<tr>
<th>Medical reason for exclusion (n)</th>
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<tbody>
<tr>
<td>Cardiac instability (12)</td>
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<tr>
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<tr>
<td>Unstable cerebral aneurysms (2)</td>
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<td>Psychological disorder/dementia (2)</td>
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<tr>
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<td>Proliferative diabetic retinopathy (1)</td>
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<td>Unstable hemodialysis (1)</td>
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<td>Non-compliance to hemodialysis (1)</td>
<td>3.8</td>
</tr>
<tr>
<td>Hemiparesis (1)</td>
<td>3.8</td>
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</tbody>
</table>

Data from 142 patients screened; 26/142 (18.3%) were excluded for the medical reasons listed.

Approaching eligible patients
It was expected that many medically eligible patients would refuse to participate in the present trial based on previous published data of exercise adherence rates in this cohort. Our investigative team ensured that every attempt was made to guide patients into the trial by overcoming their fears and reluctance to participate in a structured exercise program. Upon initial approach, each patient was given a very brief, lay description of the study. The on-site exercise physiologist addressed any questions or concerns of the patient accordingly. In our experience, recruiting a patient was commonly a 1-week-long or
2-week-long process. This process involved a high degree of rapport and trust building.

THE TRAINING REGIMEN

PRT equipment

All weight-training equipments were kept on a trolley (Figure 1) that could be wheeled around the unit, from patient to patient. The trolley was stored in a spare room in the renal unit when not in use. The PRT regimen was implemented using free-weight dumbbells (Australian Barbell Company, Mordialloc, Vic., Australia) for upper body exercises, and weighted ankle cuffs (Australian Barbell Company) for lower body exercises. Dumbbell loads ranged from 2 to 15 kg. Loading of the weighted ankle cuffs ranged from 0 to 15 kg. Additionally, Thera-BandTM tubing (Thera-Band, Akron, OH, U.S.A.) was used for one exercise targeting the hamstrings (i.e., seated leg curl).

Specific PRT exercises

Upper body exercises included the shoulder press, side shoulder raise, triceps extension, biceps curl, and external shoulder rotation (Figure 2). Lower body exercises included seated knee extension, supine hip flexion, supine hip abduction, supine straight-legged raise, and seated leg curl (Figure 2). The abdominal musculature was targeted with either bilateral straight-leg raises in a supine position or bilateral leg lifts in a seated position, depending on subject preference and level of ability (Figure 2).

Method of delivery

All PRT exercises were performed in a seated or supine position in a standard HD chair (LA-Z-BOY Pty Ltd., Moorebank, NSW, Australia). The limb containing the vascular access, forearm arteriovenous fistula (AVF), or forearm Gortex fistula was exercised immediately before each treatment session while the patient was seated in a chair in the waiting area of the unit, unless a temporary vas catheter access precluded upper body training.

Frequency, intensity, volume, and progression

Patients exercised 3 times per week during dialysis under the supervision of an exercise physiologist. During each training session, 2 sets of 8 repetitions of 10 exercises targeting the major muscle groups of the upper and lower extremities (Figure 2) were performed at a rating of perceived exertion of 15 to 17 (“hard” to “very hard”). The exercise physiologist adjusted training loads accordingly, as the strength of the patient improved with training.

Timing of the regimen

Dialysis session times ranged from 4 to 6 hr in our patients. The average duration of an intradialytic exercise session was approximately 45 min. In general, the PRT regimen was delivered before the final hour of treatment. However, subjects not prone to late-onset, dialysis-induced hypotension were exercised up to 10 min before the end of treatment. Forty of 49 (82%) patients completed the 24-week trial with 75.9% compliance to training. No adverse dialysis-related events resulted from the PRT regimen. Typically, no adjustment to the dialysis regimen was required, although blood flow rates were reduced by <50 mL/min by the renal nursing staff if the dialysis alarms were activated because of elevated arterial and/or venous blood pressures while exercising in some patients.

Evaluation of outcome measures

Outcome measures included thigh muscle cross-sectional area and attenuation (evaluated via computed tomography [CT] scan), physical tests (e.g., muscular strength, 6-min walk), anthropometrics, nutritional status, hematological indices of disease state, inflammatory cytokines, and questionnaires to evaluate depression and health-related QOL. With the exception of the CT scan, all outcome measures were collected in, or around the dialysis unit at the time of routine treatment sessions. This approach was utilized to alleviate perceived burden...
as a potential deterrent to participation. Physical measurements were completed just before (15–20 min) scheduled dialysis treatment sessions, questionnaires were delivered during treatment, and anthropometric data (e.g., height, weight, and waist and limb circumferences) were collected immediately posttreatment.

Figure 2 Progressive resistance training exercises: (a) shoulder press, (b) side shoulder raise, (c) external shoulder rotation, (d) triceps extension, (e) biceps curls, (f) double leg lifts, (g) seated knee raises, (h) knee extension, (i) straight-legged raise, (j) hip flexion, (k) hip abduction, and (l) hamstrings curl with Thera-band™.
POTENTIAL MODIFICATIONS OF THE EXERCISE PRESCRIPTION

Despite clear limitations encountered while exercising in a standard HD chair (LA-Z-BOY Pty Ltd.), postural control was strongly emphasized. Many patients were capable of moving toward the edge of the chair to facilitate technique and utilize a greater range of motion during upper body exercises, thereby optimizing the opportunity for training-induced adaptations. However, it is evident that if PRT regimens are to be included in routine care over the long term, certain modifications of the training regimen, and chair and equipment specifications will likely be required.

Large muscle groups of the upper extremity, including the latissimus dorsi and pectorals, were not sufficiently targeted with our training regimen. This was because of the fact that all upper body exercises were performed in an upright, seated position using dumbbells. A potential solution to target the chest and back musculature more effectively is to adapt resistance training devices, which optimally recruit these muscles from a seated position, to the HD setting.

There may also be a strong rationale for simply prescribing all upper body exercises just before routine dialysis treatment in the waiting area of the dialysis unit, given that it takes half the time to train the upper body bilaterally (i.e., both extremities simultaneously) vs. unilaterally (i.e., one extremity at a time). Training access for the patient remains optimized, as the PRT is still integrated into the dialysis setting, although patients must be willing to arrive early to perform this component of their training.

Four lower body exercises in our regimen were performed using weighted ankle cuffs. These exercises primarily targeted the quadriceps and thigh abductors. One additional exercise, a seated leg curl performed using Thera-Band™ tubing, targeted the hamstrings. In our experience, it was difficult to target the gluteal and calf muscle groups while seated in the standard HD chair. Additionally, while nearly all lower body exercises performed provided continuous overload stimulus throughout the training period for all patients, the knee extension exercise did not, as the weight cuffs could only be loaded with up to 15 kg, which was not challenging for many of the patients by the end of the trial. Thus, it may be favorable to develop resistance training devices, perhaps in concert with an adapted HD chair, which could more effectively recruit the lower body musculature while the patient is seated, receiving dialysis treatment.

Supervision of patients needs to be considered, given that financial restrictions in some health care settings would preclude the hiring of full-time exercise physiologists to monitor the training sessions directly. Training of on-site health care professionals, such as nurses, therapists, and dietitians who work with these patients already, to supervise the exercises would be another approach to practical implementation that we are currently planning to trial. In our experience, patients are capable of performing a significant proportion of the training program on their own. However, changing of the ankle cuffs, stabilizing the cart while performing hamstring curls, and preventing the chair from inherently rocking were all dealt with by the supervising exercise physiologist, thus limiting complete independence in the performance of PRT.

SUMMARY

Preliminary evidence from our randomized-controlled trial suggests that an intradialytic PRT program can creatively modify the health care environment, and enable HD patients to improve their health status over time with appropriate exercise training. The method outlined here is feasible within the constraints of typical outpatient HD clinic and appears to be safe and effective according to our findings. Additional robust clinical trials are needed to identify optimal modalities and doses of exercise for this cohort, for a broad range of clinical outcomes. Our methodology and future considerations, as presented, may aid in the development of future clinical trials, and the implementation of successful exercise programs within the conventional HD setting. Indeed, such efforts are required if the health status and QOL of this special patient population are to be improved.

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