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**Progressive Resistance Training During Maintenance
Hemodialysis in Patients With End Stage Renal Disease**

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Statement of Authentication

I, Danwin Chan, BHSc (Hons), BAppSc (HM), AEP, hereby declare that this thesis presents original work carried out by myself and it does not incorporate any material previously published or written by another person for a journal or for the award of another degree or diploma except where acknowledged in the text.

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Statement of Contributions to Jointly Authored Works Contained in the Thesis

Chapter 4

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Author contributions:

D. Chan – Design, data collection and management, data analysis, manuscript preparation,

B.S. Cheema – Design and manuscript review

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Published Works by the Author Relevant to the Thesis

The following publications related to the topic of investigation were co-authored by Dan Wei Danwin Chan during the PhD candidature.

Appendix 1:

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Author contributions:

B.S. Cheema – Literature search and review, manuscript preparation

D. Chan – Literature search and review, manuscript preparation

Appendix 2:

Cheema BS, Chan D, Fahey P, Atlantis E. Effect of progressive resistance training on measures of skeletal muscle hypertrophy, muscular strength and health-related quality of life in patients with chronic kidney disease: a systematic review and meta-analysis. *Sports Medicine*. 2014; 44(8): 1125-38.

Author contributions:

B.S. Cheema – Design, literature search and review, manuscript preparation, data analysis

D. Chan – Data collection, literature search and review, manuscript preparation

E. Atlantis – Design, manuscript review

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Abstract

Background: The global incidence of end-stage renal disease (ESRD) continues to rise annually. Accompanying this rise is an increase in the number of patients on hemodialysis. These trends are being driven by an unprecedented burden of hypokinetic, non-communicable diseases, and particularly the type 2 diabetes-obesity pandemic. The progression of kidney disease is associated with an exponential increase in atherosclerotic cardiovascular disease (CVD) and associated mortality. CVD is the leading cause of hospitalization and death in this cohort. As the ESRD patient population continues to grow, greater efforts must be directed toward improving patient outcomes in this cohort, including morbidity, mortality and health-related quality of life (HRQoL).

Aims: This thesis addresses several gaps related to the investigation and application of progressive resistance training (PRT) in the hemodialysis setting. The specific aims were: (i) to systematically review the extant literature on PRT in patients with ESRD, and to outline recommendations for robust clinical trials; (ii) to assess the feasibility and efficacy of including a novel customized resistance training device within a comprehensive intradialytic PRT intervention in a conventional hemodialysis unit; (iii) to investigate the effect of a 12-week intradialytic PRT intervention on measures of CVD risk, specifically, arterial stiffness (i.e. pulse wave velocity; PWV) and associated outcomes (i.e. hemodynamic, anthropometric, and hematologic).

Research Program: The research program was undertaken from March 2011 to March 2015 and culminated in a clinical trial enrolling 22 participants conducted across four dialysis centers in Adelaide, South Australia.

Overview of Chapters (Key Findings): Chapter 1 presents the background and aims of the research program. Chapter 2 and 3 present a general review of the literature and the general methodology for the clinical trial, respectively. Chapter 4 presents a systematic review of the extant literature. The evidence gathered suggests that PRT can induce muscle hypertrophy and improve aspects of physical functioning and HRQoL in this population. There is also preliminary evidence to suggest that PRT may reduce protein-energy malnutrition and CVD risk factors, including CRP, total cholesterol, triglyceride, and measures of insulin resistance in patients with or at-risk of comorbid type 2 diabetes. Chapter 5 presents on the development, feasibility and efficacy of a novel resistance exercise device used to deliver 12 weeks of intradialytic PRT. The device was developed to enable the performance of 2 upper and 3 lower body exercises, unilaterally and bilaterally, both before and during dialysis with loads of 2.5 to 59 kg. The PRT intervention was delivered without serious adverse events, resulted in $71.2 \pm 23.3\%$ adherence and significant adaptation of all training loads from pre to mid to post training (83.8% to 185.6%, all $p < 0.05$). Lower body strength ($p < 0.001$) and HRQoL sub-scales (Role-Physical, Social Functioning, Role-Emotional) significantly increased (all $p < 0.01$) and a trend toward reduced depression was noted ($p = 0.06$). No significant changes were noted in other outcomes. Chapter 6 presents on the effect of a 12-week intradialytic PRT intervention on PWV, hemodynamic and associated biomarkers in patients with end stage renal disease (ESRD). Twenty-two patients with ESRD (59% men, 71.3 ± 11.0 years, 28.5 ± 5.67 kg/m², 7 mo. to 13.5 years on hemodialysis) performed supervised full-body PRT (3 sets, 11 exercises, moderate intensity) three times per week during routine hemodialysis treatment. No significant change in log-PWV was detected between control and intervention periods [mean difference = 0 (95% CI = -0.1 to 0.1); $P = 0.58$]. Similarly, no significant change was noted in any of the secondary outcomes between the control and intervention periods.

Conclusions: Chapter 7 presents general conclusions to the thesis, as follows: (i) According to

the systematic review of the extance literature (Chapter 4) clinical trials are required to investigate a range of novel research questions related to the benefits and application of PRT in this cohort and its patient subgroups (e.g. diabetes, depression, dyslipidemia, etc.). Future studies must be of high methodological quality to inform clinical practice guidelines. (ii) According to the study presented in Chapter 5, PRT using the novel training device was feasible and improved measures of physical and psychological health and HRQoL. This device can be utilized in most dialysis centers. Future studies are required to evaluate dose-response effects of PRT prescriptions in subpopulations, and the application of PRT in standard dialysis practice. (iii) According to the study presented in Chapter 6, 12 weeks of low-to-moderate intensity intradialytic PRT did not change PWV, hemodynamic, anthropometric or hematologic measures in patients with ESRD. More research is needed to determine whether different intensities or durations of PRT can affect vascular health or other outcomes related to survival in this patient group.

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Abbreviations

Abbreviation	Full term
3RM	3 repetitions maximum
6MW	6 minute walk
ADL	Activities of daily living
AT	Aerobic training
AI	Augmentation index
ANZCTR	Australia and New Zealand Clinical Trial Registry
BMI	Body Mass Index
BP	Blood pressure
CARI	Caring for Australasians with Renal
CES-D	Center for Epidemiologic Studies Depression
Δ	Change
CHF	Chronic heart failure
CKD	Chronic kidney disease
cm	Centimeter
CV%	Coefficient of variation percentage
CL	Confidence limit
CRP	C-reactive protein
CSA	Cross sectional area
DOPPS	Dialysis Outcomes and Practice Patterns Study Program
DBP	Diastolic blood pressure
ES	Effect size
e-CFU	Endothelial colony forming units
EPC	Endothelial progenitor cells
ESRD	End-stage renal disease
EPO	Erythropoietin
GDS	Geriatric depression scale
GFR	Glomerular filtration rate
HRQoL	Health-related quality of life
HT	Healthy participants
HR	Heart rate
HDL	High density lipoprotein
IGF	Insulin growth factor
IL	Interleukin
ICC	Intra-class correlation coefficient
K/DOQI	Kidney Disease Outcome Quality Initiative
KHA	Kidney Health Australia

kg	Kilogram
Kt/V	Dialysis adequacy
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MRI	Magnetic resonance imaging
VO ₂	Maximal oxygen uptake
MD	Mean difference
mRNA	Messenger ribonucleic acid
m	Metre
mmHg	Millimeter mercury
ND	Nandrolone decanoate
NYHA	New York Hearth Association
NCT	Non-controlled trial
PCS	Physical Component Summary
MCS	Mental Component Summary
RPE	Rating of perceived exertion
%	Percentage
PASE	Physical Activity Scale for the Elderly
PPA	Physiological profile assessment
P	Placebo
PP	Pulse pressure
PWV	Pulse wave velocity
STS	Sit-to-stand
SI	Sham intervention
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Medical Outcomes Trust Short-Form 36
TC	Total cholesterol
TRN	Training
TNF- α	Tumour necrosis factor-alpha
T2DM	Type 2 diabetes mellitus
WLC	Wait-list control
WSCT	Within subject control trial



Chapter 1

Introduction

1.1 Background

The global incidence of end-stage renal disease (ESRD) continues to rise annually (1). Accompanying this rise is an increase in the number of patients on hemodialysis (1). These trends are being driven by an unprecedented burden of hypokinetic, non-communicable diseases, and particularly the type 2 diabetes-obesity pandemic (2).

The progression of kidney disease is associated with an exponential increase in atherosclerotic cardiovascular disease (CVD) and associated mortality (3). CVD is the leading cause of hospitalization and death in patients with ESRD receiving maintenance hemodialysis (1). Data suggest a 10-30 fold higher risk of CVD-related mortality versus the general population (4). As the ESRD patient population continues to grow, greater efforts must be directed toward improving patient outcomes in this cohort, including morbidity, mortality and health-related quality of life (HRQoL).

Progressive resistance training (PRT) is an anabolic form of exercise that involves challenging the skeletal muscles with unaccustomed loads, usually in the form of free- or machine weights. Clinical trials in other cohorts have consistently shown that chronic PRT interventions (>6 weeks) can counteract many impairments that accrue as a consequence of ageing and hypokinetic diseases (5). PRT is the exercise modality of choice for inducing skeletal muscle hypertrophy and enhancing bone mineral density (6, 7). These adaptations often underlie improvements in physical functioning (e.g. muscular strength), activities of daily living (8-10) and HRQoL (11-13). Accumulating evidence from other chronically diseased cohorts suggests

that PRT can also attenuate CVD risk factors [e.g., hypertension, blood lipids, visceral fat, insulin resistance, and circulating C-reactive protein (CRP)] (14-18).

1.1.1. Systematic review of the extant literature

In 2002, Headley et al (19) conducted the first study of isolated PRT in patients with ESRD. Ten hemodialysis patients were prescribed 12 weeks of PRT during non-dialysis time. Each training session consisted of 9 machine-weight exercises targetting all major muscle groups. Participants significantly improved several measures of physical functioning, including six-minute walk, maximal walking speed, sit-to-stand movement time and leg extension strength from pre to post training. Since this initial study (19), 16 clinical trials have shown that isolated PRT (>6 weeks) prescribed within or outside of routine hemodialysis treatment is safe, and can induce clinically important adaptations in patients with ESRD (20-22). Despite an accumulating evidence base, PRT and exercise training in general are not routinely prescribed in clinical practice to enhance health outcomes in this cohort. This shortcoming of clinical practice may be due to the lack of widespread awareness of the PRT in ESRD literature. Hence, a systematic review of the extant evidence base is warranted.

1.1.2 Refining the delivery of intradialytic PRT

Early studies evaluating the efficacy of PRT in patients with in ESRD prescribed PRT interventions during non-dialysis time and resulted in low participant enrollment and compliance (23). More recently, since 2006 (24), many PRT interventions have been prescribed during dialysis (25-27) in an attempt to overcome some of the barriers to exercise participation in this cohort, including lack of access and time (23). To date, the exercise equipment used to deliver intradialytic PRT interventions within clinical trials has been largely been rudimentary (28). Lower body exercises have typically been prescribed using weighted ankle cuffs (24, 27, 29-32),

and upper body exercises have either been avoided due to perceived difficulty (26), or prescribed unilaterally during dialysis in the non-fistula containing arm using elastic bands (32) or dumbbells (31), with the fistula-containing arm trained with the same exercises just prior to each dialysis session. Utilizing these rudimentary forms of equipment is cost-effective, but can compromise PRT effectiveness (28). For example, ankle cuffs typically have a low loading capacity (up to 10kg), and patients who have achieved the maximum load will experience no further overload or adaptation (28). Moreover, the use of dumbbells during dialysis restricts a patient to performing only a few exercises that do not effectively target the major muscle groups of the upper body, e.g. pectorals or latissimus dorsi (28). Experts have previously suggested a need to develop and evaluate the effects of more robust, custom-designed resistance training devices to enhance the delivery of PRT interventions in the hemodialysis setting (33). There is currently a need to develop and test the feasibility and efficacy of more refined resistance exercise equipment in the hemodialysis setting.

1.1.3 Arterial stiffness and associated biomarkers of CVD risk

Pulse wave velocity (PWV) is a measure of arterial stiffness that can be assessed non-invasively using applanation tonometry (34). Elevated PWV reflects greater arterial calcification or arteriosclerosis (i.e., lower arterial compliance) and is a strong predictor of cardiac events and CVD mortality in ESRD (35, 36) and other clinical cohorts such as non-dialysis CKD, hypertension and coronary artery disease (37). Previous studies have shown that intradialytic aerobic training can significantly reduce PWV (38). This improvement in arterial stiffness could be partially mediated by enhanced vascular repair reflected in the increased number and/or function of progenitor cells (PCs) and endothelial progenitor cells (EPCs) (39, 40).

Interventions that decrease arterial stiffness (increase arterial compliance) and increase circulating EPCs may contribute to better CVD-related survival in patients with ESRD (35, 36, 41). Current evidence suggests that PRT may mitigate CVD risk in patients with ESRD by mitigating risk factors such as blood lipids (i.e. total cholesterol and triglyceride)(42), CRP (30, 31, 43, 44), and body adiposity (27, 42) However, to date, there has been no investigation of the effect of PRT on arterial stiffness, associated biomarkers (e.g., PCs and EPCs) and other CVD risk factors in patients with ESRD.

1.2 Research Program

This research program was undertaken from March 2011 to March 2015 and culminated in a clinical trial conducted across four dialysis centers in South Australia, including the Payneham Dialysis Center, the Wayville Satellite Dialysis Center, the Hartley Dialysis Center and the Queen Elizabeth Hospital's dialysis ward.

All study procedures were completed within one center before proceeding to the next given that only the principal investigator was involved in the collection of data (i.e. recruitment of participants, assessments, and delivery of the intervention).

The customized resistance exercise device tested in this clinical trial was co-designed by the candidate based on several years of experience working as a healthcare professional in a setting that routinely prescribed intradialytic PRT with a variety of exercise equipment.

The candidate was also involved as a co-author during his candidature on two published

manuscripts: (i) a book chapter (22) on the safety and benefits of PRT across the chronic kidney disease continuum published in the first textbook on PRT in the prevention and treatment of chronic diseases (45) (candidate's authorship contribution = 50%¹), and (ii) a systematic review and meta-analysis of randomized controlled trials evaluating changes in muscle mass, strength and HRQoL across the chronic kidney disease continuum (published in *Sports Medicine*, Impact Factor: 5.2; candidate's authorship contribution = 30%²).

1.3 Aims

The overall aim of this research program was to advance the investigation and application of PRT in the hemodialysis setting.

The specific aims were:

- 1) To systematically review the extant literature on PRT in patients with ESRD, and to outline recommendations for robust clinical trials to investigate a range of novel research questions related to the benefits and application of PRT in patients with ESRD.
- 2) To assess the feasibility and efficacy of including a novel customized resistance training device within a comprehensive intradialytic PRT intervention in a conventional hemodialysis unit.
- 3) To investigate the effect of a 12-week intradialytic PRT intervention on PWV and secondary relevant outcomes (i.e. hemodynamic, anthropometric, and hematologic).

¹ Note that the candidate could not be listed as first author on this book chapter at the request of the book editors, J.T. Ciccolo and

² Other author contributions: B.Cheema 30%, P.Fahey 20% and E. Atlantis 20%

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Chapter 2
General Review of the Literature

2.1 Classifications of Renal Disease

Chronic kidney disease (CKD) is diagnosed according to the presence of kidney damage and/or decreased kidney function for 3 months or more, irrespective of the underlying cause (K/DOQI, 2002; KHA 2012; CARI, 2012). Kidney damage is determined by the presence of albuminuria, proteinuria, haematuria or structural abnormalities of the kidney determined by imaging (CARI, 2012). The classification of kidney function ranges from Stage 1 to 5 and is based on glomerular filtration rate (GFR). A reduction in GFR to less than 60 ml/min/1.73m² that persists for 3 months or more is an indicator used to diagnose CKD. At end-stage renal disease (ESRD) which is Stage 5 CKD, the GFR is less than 15 mL/min/1.73 m², indicating that the level of kidney function can no longer sustain life (1). The individual with ESRD therefore requires renal replacement therapy in the form of hemodialysis, peritoneal dialysis or a successful kidney transplant (1).

2.2 Incidence and mortality rate in ESRD

The incidence of end-stage renal disease (ESRD) continues to rise within Australia and other developed nations. Although there has been an increasing number of renal transplant operations performed in the past five decades, the number of new patients diagnosed with ESRD still exceeds the number of renal transplants by approximately four-fold (2, 3). In 2009, 772 transplant operations were performed (3), while over 2,300 individuals in Australia commenced hemodialysis treatment for the management of ESRD, raising the total number of dialysis patients to over 10,000 (4). Only 11% of all who are dialysing were on the transplant waiting list (5).

The primary factors contributing to the rising tide of ESRD include the aging demographic and chronic disease epidemics. Burgeoning rates of type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease (CVD) and underlying cardiometabolic impairments (e.g. atherosclerosis, dyslipidaemia, etc.) have increased the incidence of ESRD within Australia and worldwide (2, 6-8).

As the incidence of ESRD continues to increase, greater efforts must be directed toward improving the morbidity and mortality in this patient population. The mortality rate in hemodialysis patients is 7 times higher than in the general population (7), and two times higher than in patients with diabetes, cancer, congestive heart failure, cerebrovascular accident, transient ischaemic attack or acute myocardial attack (7). The five year life expectancy in hemodialysis patients is 34% (7).

2.3 Cardiovascular morbidity and mortality in ESRD

Atherosclerotic CVD is highly prevalent and remains a leading cause of death in patients with ESRD (9, 10). Recent data suggest that among patients commencing renal replacement therapy, approximately 34% have diagnosed coronary artery disease and 19% have diagnosed peripheral artery disease (2). The incidence rates for both myocardial infarction and stroke are 5 to 15 times higher in hemodialysis patients versus the general population (11). CVD accounts for at least one-third of deaths in hemodialysis patients (9) and cardiovascular mortality is generally 10 to 30 times higher in dialysis patients than in the general population (12-15). Hence, the prevention, management and/or treatment of CVD is essential to improving the life expectancy and HRQoL of this patient population.

2.4 Cardiovascular disease risk factors in ESRD

Traditional CVD risk factors include older age, male gender, diagnosis of T2DM, history of tobacco use, dyslipidaemia, hypertension and left ventricular hypertrophy. Many of these risk factors independently predict cardiovascular and all-cause mortality in patients with ESRD (16). However, the evidence also suggests that these risk factors alone may not identify those patients at highest risk of cardiovascular events or mortality. Interestingly, Cheung *et al.* (10) determined that these traditional risk factors predict a similar burden of CVD events or mortality in patients with ESRD as in the general population. However, notably, the data indicate a 3 to 8 times higher prevalence of coronary heart disease in ESRD (10, 12, 17, 18). Thus, the data obtained by Cheung *et al.* (10) suggest that the traditional CV risk factors may be insufficient to account for the higher CVD risk in patients with ESRD. For example, it has been suggested that renal-specific risk factors including uremia, acidosis, proteinuria, fluid overload, electrolyte imbalances, anaemia and a higher prevalence of thrombogenic factors contribute significantly to the elevated CVD risk in this cohort (10, 19).

2.5 Management of ESRD complications with exercise

Due to renal anaemia and muscle weakness complications associated with ESRD, patients are prone to fatigue and sedentariness which accelerate declines in exercise capacity (20-22). Patients with CKD, including ESRD, have a higher prevalence of physical inactivity than the non-CKD population (23, 24). When compared to established norms, ambulatory patients new to hemodialysis score below the 5th percentile for all age and gender categories (23). There is a corresponding decline in maximal exercise capacity characterised by peak oxygen uptake (VO_2)

and increased muscle wasting with deteriorating renal function over time in patients with CKD (25-27). Patients starting dialysis treatment have a physical fitness and functioning of about 50% to 70% of that of healthy subjects (28-30), thus negatively impacting even their capacity to perform activities of daily living and occupational tasks (31).

In the past four decades, substantial advances in medicine and research to reverse these complications have been achieved. In particular, the use of recombinant human erythropoietin (EPO) since the early 1990s has been successful in correcting renal anaemia; however, this treatment does not normalise peak exercise capacity (32-35). By contrast, studies investigated the efficacy of intradialytic exercise training have yielded consistent and significant effects on exercise capacity and other clinically relevant outcome measures.

In 1986, Painter *et al.* (36) conducted the first study that prescribed aerobic training (AT) during routine hemodialysis treatment. Fourteen patients performed up to 30 min of cycling three times per week during dialysis sessions. Their VO_2 improved at 3 and 6 months of training, to a similar extent (23%) as in previous studies (17.8–21%) that prescribed a longer training duration of training (8–12 months) on non-dialysis days (36). Since this seminal study by Painter *et al.* (36), several studies have further examined the effects of AT such as intra-dialytic cycling or walking on non-dialysis days and these elicited many positive adaptations, including increased VO_2 (37-41). Studies that prescribed 2 to 6 months of AT showed improvement in VO_2 by an average of 17% with or without the administration of EPO (22, 42). In more recent times, several prospective studies observed that both low physical activity level and exercise capacity are associated with increased risk of mortality in CKD (23, 43-45), thus suggesting that AT may improve survival rate by improving VO_2 directly and through modifications of various cardiovascular risk factors.

There also appears to be a shift in focus in researching the effect of exercise on maximal oxygen uptake to other physiological markers of cardiovascular health. Several intradialytic AT trials have been successful in reducing the use of anti-hypertensive medications, and improving other clinical markers including: blood pressure (46, 47), B-type natriuretic peptide (48), C-reactive protein (49), cardiac baroreflex sensitivity (50), epicardial fat layer, and serum alkaline phosphatase (a risk factor for vascular calcification) (51). These studies generally enrolled more participants and had higher rates of exercise adherence versus studies that prescribed exercise during non-dialysis time. Furthermore, intradialytic AT has been shown to significantly increase weekly phosphate removal (52) and reduce the rebound of urea, creatinine and potassium (53). The increased clearance of solutes during intradialytic AT is due to the acute dilation of the vasculature in skeletal muscle (54). These metabolic adaptations to intradialytic exercise may contribute to improve cardiovascular health.

Consequently, there is strong support to prescribe exercise during dialysis for hemodialysis patients to achieve higher exercise adoption and adherence (55, 56). Low motivation, lack of equipment, bad weather, fear of falling, a lack of time are commonly cited psycho-social barriers to participation that can be overcome by the provision of exercise advice and supervision during hemodialysis sessions (57-60). However, it should be noted that patients can be at risk of hypotension due to fluid removal during intradialytic exercise, thus precluding them from completing the amount of exercise achievable during a non-dialysis day (50). Otherwise, exercise for hemodialysis patients is generally safe, as indicated by over 28,400 patients-hours of exercise in research studies recently reviewed by Smart *et al* (42); no deaths due to exercise have been reported and the benefits derived from exercise outweighs the low risk of adverse events with appropriate exercise screening and prescription. Common adverse events include hypotensive or ischemic events.

Systematic reviews of exercise training in CKD, particularly patients on hemodialysis had reported significant improvements in aerobic capacity, muscle strength, physical functioning and HRQoL in response to intradialytic exercise (20, 42, 61). Due to the ease of prescribing aerobic exercise, particularly cycling, during hemodialysis treatment, the majority of research generated to date has been focussed on the effects of AT (20, 61).

2.6 Progressive resistance training in ESRD

PRT is an anabolic exercise modality that involves exercises which challenge the skeletal muscle to work against a resistance for a limited number of repetitions. PRT is the exercise modality of choice for inducing skeletal muscle hypertrophy, maintaining and enhancing bone health, and eliciting strength adaptations in healthy and chronically diseased populations (62). Moreover, PRT is especially important in preventing and reversing sarcopaenia and osteoporosis in older adults (63, 64). The increase in muscle strength and endurance due to PRT is associated with reduced myocardial oxygen and metabolic demand during submaximal exercise (62, 65). Consequently, time to exhaustion during a bout of submaximal aerobic exercise can increase despite a modest or no improvement in maximal aerobic capacity (65).

A systematic review conducted by Smart *et al* (42) also concluded that combined AT plus PRT interventions seem to produce a larger improvement in peak VO_2 compared with AT alone. Improvements in muscular strength and endurance through PRT can also potentially contribute to higher levels of physical activity, including greater involvement in activities of daily living, which could enhance cardiovascular and overall health and functioning (63, 66). Further, the American Heart Association (62, 65) highlighted accumulating evidence showing PRT can induce a range of adaptations that reflect improved cardiovascular health and reduced risk of

mortality. PRT prescribed in isolation has been shown to improve glucose tolerance, insulin insensitivity, blood lipid profile, blood pressure and body composition, particularly in individuals with values outside the recommended ranges (62, 65); however, additional robust studies are required to confirm these findings in patients with ESRD specifically.

Most studies that have prescribed supervised PRT during hemodialysis treatment have reported a high compliance rate of between 70% to 87%, with either nil or few acute complications during exercise (67, 68). These findings show that intradialytic PRT is safe and beneficial and contribute to better adherence than exercise prescribed during non-dialysis time (55). Further, regarding the safety of PRT in terms of cardiovascular risk, a review conducted on the use of RPT in patients with stable coronary heart disease found no reported anginal symptoms, ischemia, abnormal hemodynamics, complex ventricular dysrhythmias or other cardiovascular complications (69).

A systematic review of studies that have investigated the effect of chronic PRT interventions in patients with ESRD is presented in Chapter 4. This systematic review suggest that there is currently a lack of research on the effect of PRT on traditional cardiovascular risk factors, including both hemodynamic and hematological outcome measures pertinent to cardiovascular health. Thus, future research should focus on filling this gap of understanding the holistic physiological effects of RT in ESRD.

2.7 Progressive resistance training during hemodialysis treatment

Early studies evaluating the efficacy of PRT in patients with ESRD prescribed PRT interventions during non-dialysis time and resulted in low participant enrollment and adherence a

(55). More recently, since 2006 (70), a number of PRT interventions have been prescribed during dialysis (67, 71, 72) in an attempt to overcome some of the barriers to exercise participation in this cohort, including lack of access and time (55). This evidence base suggests that intradialytic PRT can improve many important aspects of health status (61). However, the delivery of the PRT in this setting must be refined to elicit better health adaptations in patients and enable more seamless translation to standard clinical care (73).

To date, the exercise equipment used to deliver intradialytic PRT interventions within clinical trials had been largely rudimentary (73). Lower body exercises have typically been prescribed using weighted ankle cuffs (67, 72, 74), and upper body exercises have either been avoided due to perceived difficulty (71), or prescribed unilaterally during dialysis in the non-fistula containing arm using elastic bands (75) or dumbbells (76), with the fistula-containing arm trained with the same exercises just prior to each dialysis session. Utilizing these rudimentary forms of equipment is cost-effective, but can compromise PRT effectiveness (73). For example, ankle cuffs typically have a low loading capacity (up to 10kg), and patients who have achieved the maximum load for a PRT exercises will experience no further overload or adaptation (73). Moreover, the use of dumbbells during dialysis restricts a patient to performing only a few exercises that do not effectively target the major muscle groups of the upper body, e.g. pectorals or latissimus dorsi (73). Experts have previously suggested a need to develop and evaluate the effects of more robust, custom-designed resistance training devices to enhance the delivery of PRT interventions in the hemodialysis setting (77).

To our knowledge, there have been only two studies that have implemented the use of novel resistance training equipment in the hemodialysis setting (71, 78). However, both devices were limited to targeting the lower body musculature only with either one (71) or a few

movements (78). Upper body musculature was not targeted by these devices, and this has been identified as a major limitation of PRT interventions prescribed to date (73).

2.8 Arterial stiffness in ESRD

Arteriosclerosis and atherosclerosis are pathological conditions and antecedents to CVD. Arteriosclerosis is the stiffening of the arteries and/or arterioles while atherosclerosis refers to the deposition of fats, cholesterol and other substances resulting in intimal plaque formation that can restrict blood flow (79, 80). Unlike atherosclerosis, arteriosclerosis affects both the intimal and medial layers of the arteries, characterised by fibrous intimal thickening and calcification of the media and internal elastic lamina (79). The arterial hypertrophy and narrowing of the arteries due to these pathological states contributes to hypertension, left ventricle hypertrophy and congestive heart failure, ultimately predisposing individuals to cardiovascular events and mortality (79, 81). Both traditional and renal-specific CVD risk factors contribute to arteriosclerosis and atherosclerosis in patients with ESRD (82). Therefore, assessing the severity of arteriosclerosis and atherosclerosis may be essential to assessing and abating CVD in this cohort.

Although arteriosclerosis and atherosclerosis commonly co-exist (83, 84), arteriosclerosis can exist without clinically evident atherosclerosis and its early detection is important for averting CVD (85, 86). The extent of arterial calcification or arteriosclerosis is directly proportional to arterial stiffness which can be measured non-invasively by using applanation tonometry (87). This method for evaluating arterial stiffness yields two parameters: the pulse wave velocity (PWV) and the augmentation index (AI) (88). PWV is a measure of arterial stiffness derived through the Moens-Korteweg equation, $PWV = \sqrt{(Eh/2R\rho)}$, where E is Young modulus in the circumferential direction, h is wall thickness, R is vessel radius, and ρ is the

density of fluid (89). The PWV is related to vessel distensibility and a faster PWV denotes a stiffer vessel. The AI is a composite measure of arterial stiffness and timing of wave reflection (89). It is quantified as the rise in pressure from the first systolic shoulder to the peak systolic shoulder as a proportion to the pulse pressure (i.e. the difference between systolic and diastolic blood pressure). This rise in pressure is known as augmentation pressure and it is mainly due to the reflected waves of the forward pressure pulse generated by ventricular ejection. A higher AI denotes a stiffer vessel.

The assessment of PWV has been well-validated in patients with ESRD (88), and PWV is a strong, independent predictor of cardiovascular and all-cause mortality in this cohort (90-93). For example, Blacher *et al.* (90) divided their ESRD study population into 3 tertiles based on the aortic PWV and found that the upper third tertile had nearly 6 times (95% CI, 2.3 to 15.5) the incidence of cardiovascular mortality as compared to the lower third. Further, Guerin *et al.* (92) found the aortic PWV to be a better predictor of mortality than blood pressure (BP) in patients with ESRD. Notably, many of the patients in this study who died during the follow up period were characterised by elevated PWV despite a reduction in mean BP due to anti-hypertensive medication usage.

2.9 Effect of aerobic training on arterial stiffness in ESRD

Three recent clinical trials that prescribed AT showed preliminary evidence that exercise can improve the PWV and the AI in patients with ESRD (94-96). One of these studies prescribed AT during non-dialysis time (95), while the other two prescribed AT during routine hemodialysis treatment (94, 96).

Mustata *et al.* (95) conducted an uncontrolled trial that prescribed AT during non-dialysis time in 11 hemodialysis patients. All patients performed AT on recumbent bikes and/or treadmills at an intensity of 60 to 80% of the maximal heart rate elicited during a baseline stress test. Exercise sessions were completed twice weekly for 3 months and each session was one hour in duration, including a 5-10 minute warm-up and cool-down period. The patients who completed the intervention significantly improved their AI (17 ± 3 to 12.2 ± 3 , $p=0.01$). The improvement in AI was accompanied by an improvement in pulse pressure (64 ± 7 to 57 ± 6 , $p<0.05$) with both adaptations indicating reduced arterial stiffness. However, in a follow-up assessment completed one month after the cessation of the AT intervention, AI and pulse pressure regressed to baseline values (95). Mustata *et al.* (95) concluded that patients with ESRD who engaged in an ongoing AT program could derive reductions in arterial stiffness, as indicated by reductions in AI and pulse pressure. PWV was not measured in their study.

In another study, Toussaint *et al.* (94) conducted a prospective, crossover trial in 19 hemodialysis patients. The exercise program consisted of 30 minutes of intradialytic exercise cycling performed three times per week. The patients were randomised into an exercising group and a non-exercising group for an initial 3-month training period. This was followed by 1-month of detraining (wash out) and a second 3-month, cross-over period. The patients were instructed to exercise for approximately 30 minutes at a self-selected exercise intensity (i.e. to tolerance). After the initial 3-month period, a near-significant improvement in the PWV ($p=0.07$) was noted in the exercising patients while the non-exercising patients showed no change ($p=0.31$). Following the second 3-month training period, the patients now allocated to the exercise intervention showed a trend toward improved PWV ($p=0.11$) while the patients allocated to no exercise showed a trend toward regression ($p=0.19$). When the whole study cohort was analysed, the mean PWV was significantly improved (9.04 vs 10.16 m/s, $p=0.008$) with 3-month of AT compared with no training. The magnitude of this improvement in the PWV (1.0 m/s) was

considered clinically significant (92), and this improvement was concomitant with a trend toward improved AI ($p=0.062$). The authors concluded that prescribing AT during hemodialysis should be a standard practice in order to maintain improvements in arterial compliance (i.e. reduce arterial stiffness) and reduce CVD risk and mortality.

Koh *et al.* (96) conducted a RCT by allocating 46 patients to intra-dialytic exercise ($n=15$), home-based exercise ($n=15$) or usual care ($n=16$). Both exercising groups performed exercises three times per week for 6 months, while the usual care group did not exercise. The intradialytic exercise group engaged in an exercise cycling intervention and progressively increased the duration of each session from 15 to 45 minutes. The intensity of AT was prescribed at a rating of perceived exertion (RPE) of 12 – 13. Resistance of the cycle ergometer was increased if heart rate was low relative to the prescribed RPE. Similarly, the home-based exercise group performed a walking intervention that progressed from 15 min to 45 min per session at an RPE of 12 to 13. Arterial stiffness measures, including PWV and AI did not significantly improve in either of the exercise groups over time when compared to the usual care control group (all $p>0.05$). In addition, the exercising patients did not significantly improve the secondary outcome measurements, which included surrogate markers of cardiovascular health such as the six-minute walk.

Study design limitations may have contributed to the disparate findings of these three studies (48, 95, 96). Among the three studies, only Koh *et al.* (96) showed no effect of AT. However, it should be noted that in this study (96), the authors provided information about the benefits of physical activity to the control group (citing ethical reasons), which may have contributed to the documented 36% increase in physical activity in the control group. This could have compromised the nature of the control group (i.e. no exercise) making it unreasonable to draw conclusions about the effectiveness of the AT intervention.

Due to the small sample size of the randomised crossover study of Toussaint *et al.* (94), a significant change in the arterial stiffness measurements between the exercise period to the non-exercise period was only noted when both groups were analysed as a whole. However, no significant change was found between the exercise group and the non-exercise group during the first 3 months. On the contrary, Mustata *et al.* (95) conducted a non-controlled trial that found positive changes in arterial stiffness characterised by improved AI. Their patients were on the average older than those in the other two studies and this could be a factor of the greater improvement in arterial stiffness as older participants may have greater potential for exercise-induced adaptation than younger participants.

The difference in their findings may also be attributed to differences in exercise protocols. Koh *et al.*'s (96) progressed the exercise volume and intensity at a slower rate than the other studies and this may have limited the potential cardiovascular benefits. Both Mustata *et al.* (95) and Toussaint *et al.* (94) prescribed a longer duration of training per session (i.e. 30 to 50 min). Mustata *et al.* (95) had the patients exercise at a higher intensity level than Koh *et al.* (96) while Toussaint *et al.* (94) had the patients self-select the intensity level. When Koh *et al.* (96) compared the average work performed per session by their exercising patients, it was lower than the exercise group in the study by Toussaint *et al.* (94). Thus, the patients of Toussaint *et al.* (94) could have exercised at a higher intensity on average when compared to the patients of Koh *et al.* (96).

Given the heterogeneity of exercise protocols and the lack of robust clinical trials, further investigations with sufficient sample sizes, and appropriate modalities, quantity and intensity of exercise need to be conducted to elucidate more clearly the effects of AT on measures of arterial stiffness (i.e. AI and PWV) in patients with ESRD. The limited number of studies available to

date do however suggest that arterial stiffness can be altered favourably by AT prescribed at a moderate intensity for a minimum duration of 3 months.

2.10 Effect of resistance training on arterial stiffness in apparently healthy adults

Although RT has consistently been shown to elicit muscle hypertrophy, and increase muscular strength, functional fitness and HRQoL in ESRD (97), no study has yet investigated the effect of RT on arterial stiffness and the burden of CVDs in this cohort. However, several studies have investigated the effect of RT on arterial stiffness in the general population and in patients with diabetes and chronic heart failure.

Recently, a meta-analysis was conducted on randomised controlled trials that examined the effect of moderate and high intensity RT on arterial stiffness in healthy adults (98). Eight studies ($n=193$) were included in the meta-analysis, with five of these studies enrolling participants younger than 40 years. The findings of the review indicated that RT significantly increased measures of arterial stiffness (PWV or carotid beta index) by a pooled mean difference of 10.7% change ($p<0.001$). Subgroup analysis revealed only high intensity RT ($>70\%$ 1RM) and not moderate intensity (40-70% 1RM) RT was associated with an increase in arterial stiffness measures. All four studies that prescribed high intensity PRT induced increases in arterial stiffness and these might be due to a high sympathetic vasoconstrictor activity elicited during heavy, loaded exercise (99). Further, when performing high intensity training, participants are often obliged to lift slowly, due to the heavy resistance, if not given instruction to do otherwise. Okamoto *et al.* (100) found that high intensity RT with slow lifting increases the PWV but this effect is not seen when the lifting phase of the movement is performed quickly, followed by a slow lowering (eccentric) phase. As most studies did not report the muscular contraction

duration (i.e. time under tension), it can only be speculated that this is a confounding variable that could affect vascular adaptation.

Although this meta-analysis indicated a negative effect of RT, the authors suggest that the magnitude of the increase in arterial stiffness is unlikely to be clinically adverse, especially in young adults with low baseline levels of arterial stiffness. Moreover, two out of three reviewed studies that had middle-aged (>40 years old) adults performing moderate intensity RT did not show any effect (positive or negative) on arterial stiffness (101-103). The increase in arterial stiffness associated with RT has been shown to revert to baseline values after detraining (104, 105). Other studies conducted by Okamoto et al have shown that healthy adults who performed low intensity RT (50% 1RM for 10 weeks) (106) or lower-limb training instead of upper-limb training (107) can either improve or have null effect on arterial stiffness measured by brachial-ankle PWV.

Further, combined AT and RT has been shown to have no effect on measures of arterial stiffness in young men (105). It is important to note that this meta-analysis was limited to the healthy general population and did not include studies that prescribed light intensity RT (<30% 1RM) or RT in older adults (>65 years). The findings of the review should therefore not be extrapolated to chronically diseased populations without direct investigation.

2.10 Effect of progressive resistance training on arterial stiffness in chronic diseased patients

A few recent research studies have investigated the effect of RT on vascular function or vascular dimensions in patients with overt cardiovascular diseases and risk factors apart from

ESRD. A RCT conducted by Maiorana *et al* (108) randomised 36 patients with chronic heart failure (NYHA class 1-3) to 12 weeks of RT, AT or a no training (control) group. Thrice weekly exercise training was prescribed in the RT and AT groups. For RT, the intensity ranged from 50 to 70% with work-rest ratio at 2:1 (60:30 seconds) for the first 6 weeks to 1:1 (45:45 seconds) for the second 6 weeks. Both exercise training modes increased maximal exercise capacity (peak VO₂) and brachial diameter, but only RT reduced brachial artery wall thickness with a consequent reduction in wall:lumen ratio. Since the RT exercises prescribed were predominantly for the lower limbs, the findings suggest that RT can induce a positive effect on systemic vascular health. Whether this translates to a reduction in aortic or brachial-ankle arterial stiffness need to be confirmed.

In overweight adults with T2DM, an intervention consisting of an initial 2-month supervised laboratory-based RT program, followed by random allocation to 12 months of RT in either a community fitness center or at home has shown promising preliminary results on endothelial function (109). The endothelium secretes vasoactive substances, primarily vasodilator nitric oxide, to regulate vascular smooth muscle tone and blood pressure in coronary and peripheral arteries (110, 111). Consequently, a degree of arterial stiffness or atherosclerosis may be mediated or precipitated by endothelial dysfunction (111, 112). The initial 2 month supervised RT program was performed twice weekly and involved 8 exercises targetting the major muscles groups. The intensity (loading) was progressively increased from 50% to 85% of 1RM. Three sets of 8 repetitions were performed for each exercise. The participants who were allocated to a fitness center continued with a similar RT program 2 to 3 times weekly while participants in the home-based group were given one hand weight to perform upper body RT with the same frequency as the other group. Endothelial function, measured using a laser Doppler flow technique, improved in both exercise groups with no between-group differences observed after

the 14-month training programs. Endothelial function was also assessed after the first 2 months but no significant change was detected in either group. There was no control group in this study.

2.11 Effect of resistance training on blood pressure in ESRD

Although prevention of renal function decline is no longer necessary in patients with ESRD, blood pressure continues to be closely managed clinically to curb the high risk of CVD and related cardiovascular morbidity and mortality in this population. Hypertension in ESRD is associated with higher relative risk of left ventricular hypertrophy (LVH), chronic heart failure (CHF) and ischaemic heart disease while low blood pressure is also independently associated with mortality (113). Drugs that inhibit the renin and/or angiotensin II production have been shown to be effective in clinical trials (114) and are currently recommended within clinical practice guidelines in ESRD due to their positive cardiovascular effects including improvements in endothelial function, reduction in PWV and sympathetic nerve activity, and regression of LVH (115). The other key factor in blood pressure management in this cohort is fluid status and the National Kidney Foundation has suggested that predialysis and postdialysis blood pressure goals should be <140/90 mmHg and <130/80 mmHg, respectively (115).

In the Cochrane review on the efficacy of exercise in CKD (20) it was determined that no study to date has specifically assessed the effect of isolated RT on resting systolic and diastolic blood pressure. More recently published RT intervention studies have also not done so (74, 116, 117). However, the review found that 5 studies prescribing a combined AT plus RT intervention significantly decreased both resting systolic BP (186 participants: mean difference 5.80 mmHg, 95%CI=1.19, 10.41) and diastolic BP (229 participants: mean difference 3.77 mmHg, 95%CI=1.61, 5.94). The review also reported that exercise training with an intensity level of

greater than 60% of maximal effort significantly reduced both SBP and DBP. In normotensive and hypertensive populations with no other concomitant disease, a meta-analysis of RCTs that prescribed RT revealed a mean difference in resting SBP of -6.0 mmHg (95% CL -10.4 to -1.6) and resting DBP of -4.7 mmHg (95% CL -8.1 to -1.4) when weighted by the reciprocal of the variance for the blood pressure change (118).

In patients with ESRD, the impact of RT prescribed in isolation on blood pressure and the underlying mechanisms contributing to blood pressure regulation remains unclear. A known complication of ESRD is cardiac autonomic neuropathy which may be characterised by increased plasma dopamine and norepinephrine, reduced heart rate variability and abnormal I-metaiodobenzylguanidine, which suggest increased cardiac sympathetic and decreased parasympathetic activity at rest (119). As hypertension can be due to elevated sympathetic tone (120), a potential way exercise training can affect blood pressure in patients with ESRD is its effect on autonomic activity. In a 10 month study of thrice weekly, 90 minutes, moderate intensity (RPE 13/20) AT conducted by Kouidi et al (121), there was a significant reduction in heart rate variability which indicates increased cardiac vagal activity. Similar increase in heart rate variability was also shown in a 6 month AT study conducted by Deligiannis et al (122). However, it was unclear whether these results were associated with a change in systolic or diastolic blood pressure, as these outcomes were not assessed.

2.12 Effect of resistance training on inflammation in ESRD

Inflammation is recognised to underlie the inception and development of atherosclerosis, from the expression of adhesion molecules by endothelial cells, adherence and penetration of leukocytes into the intima, development of fatty streaks and complex plaque, blocking of creation

of new collagen fibers, stimulating the destruction of existing collagen that contributes to an increased risk of thrombosis (123). Unlike acute inflammation which is a normal immune response to contain infection or trauma, chronic and systemic inflammation is harmful and can lead to end organ and vascular damage (124). Systemic inflammation is also linked to malnutrition, protein-energy wasting, endocrine disorders, depression and vascular calcification (125); these conditions are prevalent in uremia, CKD and ESRD (126). Furthermore, inflammation is also a strong prognostic indicator of sudden death in ESRD patients (127).

In general, CKD patients are characterised by elevations in markers of chronic inflammation such as CRP, IL-6 and TNF- α . In hemodialysis patients, these markers strongly predict survival (126, 128). CRP is a biochemical by-product that hepatocytes produce in response to IL-6 elevations during acute inflammation. It is the most widely used and accepted inflammatory marker of CV risk and due to its 19-hour half-life, it is easy to measure in circulating blood (125). CRP is a strong predictor of cardiovascular morbidity and mortality in patients receiving hemodialysis (128).

Preliminary observations of ESRD cohorts showed that inflammatory marker CRP is inversely correlated with self-reported (129) and objectively measured physical activity level (130). However, it remains unclear whether the level of CRP is a causative or the result of muscle catabolism and subsequent change in physical function and activity level (125). Among studies that have prescribed RT in isolation, Kopple et al (131), who prescribed only lower body RT, showed no change in CRP while two studies by Cheema et al (76, 132) that prescribed full body RT showed significantly decreased CRP. However, despite a reduction in CRP, a subsequent analysis of the same cohort of patients found no change in pro- and anti-inflammatory cytokines, including IL-1 β , TNF- α , IL-6, IL-8, IL-10 and IL-12. Similarly, AT studies in ESRD have shown conflicting results, with some studies reporting no change in inflammatory cytokines IL-6 (133)

and CRP (51, 94, 134) while others found a significant decrease in CRP after training (49, 135, 136). There was no obvious indication to identify whether patient characteristics, study design, exercise duration or intensity level prescribed between these studies were the cause of the conflicting results. Nevertheless, the observed relationship between CRP level and physical activity level (PAL) suggest that higher physical functioning or physical activity level may result in lower CRP level. Thus, future studies should consider prescribing an RT regimen that is comprehensive and targets the major muscle groups of the upper and lower body, similar to the intervention prescribed by Cheema et al (76).

2.13 Effect of resistance exercise training on endothelial progenitor cells in ESRD

Endothelial function is crucial to regulating arterial vascular tone, permeability and angiogenesis (137). Endothelial dysfunction is a major factor that contributes to increased arterial stiffness and the development of atherosclerosis (138). The integrity and function of the endothelial cells are dependent on a critical balance between the cells' degeneration and regeneration. Circulating cells derived from bone marrow that are identified as endothelial progenitor cells (EPCs) are a key factor to the maintenance and repair process of the damaged endothelium (139-141). EPCs are mobilised from bone marrow during cytokine stimulation and ischemic injury, homing in on the ischemic tissue, and contribute to neovascularisation and angiogenesis (139, 141-143).

When metabolic and cardiovascular risk factors are present, the integrity and function of the vascular endothelium are compromised (144-146). In patients with cardiovascular risk factors, higher levels of circulating EPCs are associated with cardiovascular event-free survival, and lower risk of cardiovascular morbidity and mortality (147, 148).

Several studies have reported either or both decreased numbers of circulating EPCs and impaired angiogenic function in patients with ESRD (149-153). Most notably, Choi et al (149) determined that patients with ESRD have a lower number of circulating EPCs, lower endothelial colony forming units (e-CFU), and impaired EPCs mobilisation and incorporation into endothelium when compared to healthy peers (149).

No data currently exist on the effect of RT on circulating EPCs in healthy adults or patients with chronic diseases, including ESRD. The possibility of RT increasing EPCs numbers can only be drawn from preliminary findings of AT effect on EPCs, especially in patients with ESRD. Several studies have emerged in the past decade showing that AT can have a positive influence on EPCs, both acutely and chronically, in healthy people and patients with coronary artery disease (154-159).

Only one study to date has investigated the effect of AT on EPCs in patients with ESRD. In a non-randomised control study by Manfredini *et al* (160), hemodialysis patients (n=14) were prescribed a 6-month moderate intensity AT intervention. The exercise protocol consisted of two 10-minute walking sessions per day at 50% of the patient's maximum treadmill speed, performed at home on at least the non-dialysis days of the week (i.e. at least 3 times per week). Maximum treadmill speed was re-evaluated and updated every month and walking speed was adjusted accordingly. When the exercise group was compared to a control group (n=8), no difference was found in circulating EPCs (CD34+AC133+VEGFR2+) and e-CFU from pre- to post-intervention although the exercise group significantly increased e-CFU within-group from baseline. e-CFU was also significantly correlated with 6-minute walking distance ($r=0.75$, $p=0.002$).

The lack of change in circulating EPCs numbers and e-CFU between groups in the Manfredini et al study (160) may be explained by the detrimental effect of uraemia *in vivo*.

Jourde-Chiche et al (161) demonstrated 24-hour incubated myeloid EPCs apoptosis increased by 81% ($p < 0.01$) after incubation with uremic serum from HD patients compared with normal serum from healthy subject. Among other uremic toxins tested, indole-3 acetic acid was identified to increase apoptosis of CD133+ cells in vitro by 38% and was negatively correlated with CD34+CD133+ immature progenitor cell numbers (161). The results indicated that EPCs number can be reduced by the detrimental effect of uremia on progenitor cells and hence its differentiation into EPCs. As e-CFU is enumerated in a non-uraemic in vitro condition in Manfredini et al' study, there is a possibility that exercise could have improved EPCs capacity to proliferate if it is in a non-uraemic environment. However, Jourde-Chiche et al (161) also showed that the addition of EPO in vitro completely reverse the effect of indole-3 acetic acid on myeloid EPCs apoptosis. In their HD patients, EPO 'good responders' (defined as patients with a lower ratio of EPO weekly dose to hemoglobin level and less than the median value) had more CD34+CD133+ progenitor cells than EPO 'poor responders'. Since EPO therapy may reduce anemia associated with kidney disease and hence improve maximal exercise capacity (54), this may be a contributory factor for the significant correlations shown by Manfredini *et al* (160, 162) between circulating EPCs and physical function measures including a 6-minute walk test, maximal treadmill speed and physical functioning score. It remains unclear whether exercise training can further increase EPCs numbers. Future research is necessary to determine also whether RT can have a similar positive effect on EPCs numbers and related outcomes including arterial compliance.

2.14 Effect of resistance exercise training on blood lipids in ESRD

Most research has measured the effect of AT, rather than RT, on lipid profile in patients with CKD or ESRD. The results of studies on the effect of AT have been mixed. Goldberg et al

(163, 164) reported decreased triglycerides in two non-controlled trials (NCT). Both Goldberg *et al*'s studies and a separate study conducted by Eidemak *et al* (165) have also reported increased HDL cholesterol. A recent controlled trial enrolling patients with early stage CKD has shown improvements in HDL cholesterol, LDL cholesterol and triglycerides but both its AT and control groups also received diet therapy which may have amplified the effect of exercise on lipid profile yama (166). Conversely, other uncontrolled studies (36, 167, 168) and RCTs (165, 169) that prescribed AT in patients with CKD or ESRD reported no change in triglycerides (165, 169), total cholesterol (TC) (165, 169), and HDL cholesterol (169). There is little indication that RT can positively alter the lipid profile in ESRD. A recent small study that randomly assigned male HD patients to either AT (10-30min of intradialytic cycling at RPE 12-16) or RT (knee extension-flexion and hip abduction-adduction at RPE 15-17) for 8 weeks did not find any change in lipid profile and BMI when in either training group compared to the control group.

One speculated reason for the lack of change in lipid profile secondary to RT may be due to a lack of change in body composition or mass. A meta-analysis of RCTs on the effect of RT on lipids in adults with and without chronic diseases (including diabetes and CVD) found significant improvements in TC, TC to HDL-C ratio, non-HDL-C, LDL-C and triglycerides but not HDL-C (170). The meta-analysis also reported that reduced BMI was associated with improvements in triglycerides, HDL-C, TC to HDL-C ratio and non-HDL-C (TC minus HDL-C). Positive association between changes in HDL-C and lean body mass and negative associations between changes in upper body strength with both TC and non-HDL-C were also found. Hence, the current evidence suggests that unless RT results in changes in body composition or body weight, lipid profile is unlikely to be altered. Such associations need to be verified in patients with ESRD.

2.15 Effect of resistance training on skeletal muscle and physical function in ESRD

Patients with ESRD are commonly found to suffer skeletal muscle wasting and dysfunction, and lower cardiorespiratory fitness compared to healthy individuals, thus resulting in reduced exercise tolerance (59, 171). Consequently, these physiological maladaptations promote or reinforce a sedentary lifestyle in this population which can lead to further muscle atrophy (172, 173) and other physiological and functional impairments (22). The potential causes of skeletal muscle wasting in ESRD are complex with multiple contributing factors such as metabolic acidosis, comorbidities, corticosteroid usage, proinflammatory cytokines, oxidative stress, insulin resistance and dialysis treatment (174-176).

Protein-energy malnutrition or wasting, characterised by skeletal muscle wasting and low visceral protein stores, is strongly associated with a high mortality risk in patients with ESRD receiving hemodialysis treatment (177-179). Low cardiorespiratory fitness (43), low PAL (44) and low exercise frequency (45) have all been associated with lower survival rate. These observed relationships thus suggest that by exercise training, these parameters can be altered favorably, which may result in increased survival.

A 2011 Cochrane review by Heiwe et al (20) on exercise training for adults with CKD analysed and found that regular RT significantly increased muscle strength (4 studies, 153 participants, SMD -0.6, $p=0.0003$) (61, 68, 72, 180) while cardiovascular exercise training (4 studies, 165 participants, SMD -0.23, $p=0.19$) (96, 181, 182) and mixed cardiovascular with RT (183, 184) did not.

Despite the physiological limitations associated with ESRD, studies have consistently shown that muscular strength and muscle composition can be altered positively and simultaneously through the prescription of RT. A recent RCT conducted by Kirkman et al (71)

prescribed 12-week intradialytic leg press resistance exercise, thrice per week, for ESRD patients using a novel machine which utilised a series of elastic bands to provide a maximum resistance equivalent to 200 kg. The participants were prescribed three sets of eight to ten repetitions at 80% of their predicted 1-repetition maximum load with 2-minute rest period between sets. Training load was progressively increased with strength adaptation. The HD patients who received RT showed clinically and statistically significant improvements in both thigh muscle volume (evaluated via magnetic resonance imaging (MRI) (Mean Difference = 193 [95% CI = 63 to 324 cm³) and knee extensor strength (Mean Difference= 56 [95 % CI = 15 to 98 N) compared to control. The changes in strength and muscle volume in response to RT were of similar magnitude in HD patients as in healthy participants.

In another RCT that prescribed 12-week, thrice per week, high intensity intradialytic RT involving most major muscle groups in upper and lower extremities, Cheema *et al.* (67, 76, 185) found statistically significant improvement in total body muscular strength, mid-thigh muscle quality (evaluated by muscle lipid content, i.e. attenuation), mid arm circumference and clinically significant improvement in mid-thigh muscle cross-sectional area (CSA) (evaluated by computed tomography) in the exercise group compared to control group. Their exercise protocol was comprised of two sets of eight repetitions for each exercise performed at a RPE of 15-17/20 (“hard” to “very hard”). Free weights dumbbells were utilised for upper body exercises while weighted ankle cuffs and elastic tubing were utilised for lower body exercises. The limb containing the vascular access was exercised just prior to the dialysis session while all other exercises were performed while the patient was in a seated or supine position receiving dialysis. In a follow up study, Cheema *et al.* (67) had also noted that an additional 12-week of intradialytic RT can induce greater gains in muscle CSA.

In another intradialytic exercise trial, Johansen *et al.* (70) double-blinded and randomised 79 patients with ESRD into four groups. The patients would receive weekly anabolic steroid (nandrolone decanoate) or placebo injections, with or without 12 weeks of RT intervention. The intervention involved performing five lower limbs exercise using ankle weights, thrice weekly while on dialysis. Training intensity began at two to three sets of 10 repetitions at 60% of 3 RM and was progressed as patients' strength improved. Quadriceps muscle CSA (evaluated by MRI) increased in the two groups of patients that completed 12 weeks RT (RT + placebo ($p=0.02$) and RT + nandrolone ($p<0.0001$)) compared to the control group. There was no significant improvement in total lean body mass (evaluated by DEXA) which may be attributed to the prescribed RT targeting only the lower limbs. The effect of RT on muscle and body composition was ascertained by Chen *et al.* (72) who prescribed a similar lower-body intradialytic RT intervention but beginning with an intensity of 60% of 1RM noted significant increases in leg and whole body fat-free mass after approximately six months of twice weekly RT.

It is important to note that several studies that prescribed RT with even lower intensity RT compared to Johansen *et al.* (68) and Chen *et al.* (72) did not find any significant change in maximum strength (measured as 1RM) (116), total lean body mass (116, 131) or physical function measures such as 6 minute walk (6MW) (75, 186). Thus, with the current evidence, positive muscle adaptations can occur in ESRD. The level of exercise duration, intensity, volume and progression similar to the study of Johansen *et al.* (68) may be the minimum dosage required to elicit positive adaptation.

Although muscle quantity and strength, and muscle oxygen extraction are associated with functional capacity in HD patients (187-190), elicited improvements in muscle strength or muscle volume due to RT may not necessarily translate to an improvement in physical function outcome measures *per se*. Kirkman *et al.* (71) reported improvements in thigh muscle volume and leg

extensor strength but no significant change in 30 s sit-to-stand (STS) and 6MW. By contrast, Chen *et al.* (72) reported concurrent improvements in knee extensor strength, STS time, self-perceived physical functioning and activities of daily living versus a sham exercise group whereas, Cheema *et al.* found an increasing trend but no significant change in 6MW (76). The lack of change despite the high intensity of RT may be due to the functional measures being less sensitive to direct measures or that the measures are also dependent on other physiological factor such as aerobic capacity (e.g 6 MW), muscular endurance (e.g 30s STS), and agility and dynamic balance (e.g 8-ft up and go) rather than only muscle strength (191). Therefore, traditional progressive RT does not appear to improve these other outcomes consistently in ESRD. However, in studies combining RT with AT (59, 183, 184), surrogate measures of cardiovascular fitness such as 6MW (67, 192-194), and other measures of physical functioning such as gait speed (193) and STS movement time (181, 193, 194) seem to consistently improve, thus suggesting the efficacy of AT as an adjunct to RT.

There is also preliminary evidence that when RT is combined with balance training, falls risk can be reduced. Bennett *et al.* (195) prescribed eight weeks of hip, knee and ankle strengthening exercises, static and dynamic balance exercises to 24 hemodialysis patients. The strength exercises were performed while on dialysis while the balance exercises were performed before or after dialysis. The short form Physiological Profile Assessment (196), which is a battery of tests on factors considered most crucial to falls risk, was utilised pre- and post-intervention. The factors evaluated include vision edge contrast sensitivity, hand reaction time, knee joint proprioception, quadriceps strength and standing postural sway on foam board. The study found significant improvements in the Physiological Profile Assessment overall score, reaction time and quadriceps strength (195). As the falls injury rate in dialysis patients is four times higher and post-hip fracture mortality is twice as high compared to age-matched

population, there is strong incentive for dialysis patients to perform strength and balance exercises to improve physical function and reduce falls risk.

It is unclear whether the form of resistance applied is a factor that affects the efficacy of RT in modifying muscle. Elastic resistance band/tubing (186), pneumatic resistance (116), weights machine (71, 192), and free-weights (including ankle cuff weights) (67, 68, 72, 76) have all been utilised in previous studies with the latter two being the common mode of RT prescriptions in most studies successfully inducing improvements in muscle strength or composition.

2.16 Effect of resistance training on quality of life and depression in ESRD

HRQoL is commonly defined to include three domains of health (physical, psychological and social), with each domain consisting of diverse components (197). Broader aspects of HRQoL in populations with chronic illnesses can also include perceptions of illness burden, happiness and life satisfaction, satisfaction with care (198, 199) and spirituality in coping (200, 201). It is relevant for health professionals to measure HRQoL due to its good prognostic value of hospitalisation, morbidity and mortality, especially in elderly dialysis patients (202, 203). The association between better HRQoL and survival rate is especially prominent in elderly dialysis patients. De Oreo *et al.* (204) assessed HRQoL of 1,000 dialysis patients using Medical Outcomes Trust Short-Form 36 (SF-36) and found that, with each five-point increase in physical component summary (PCS) score of SF-36, the possibility of survival after 2 years was increased by 10%. Further, a five-point increase in mental component summary score resulted in a 2% to 5.8% increase in survival. This showed that the domains of health are interdependent of one another and HRQoL can be considered a composite assessment of broad aspects of health

perception that may be otherwise overlooked by physiological or physical assessments. The measurement of HRQoL is therefore applicable in determining the efficacy of treatments or therapies, such as exercise, and their net benefits beyond physiological improvements (203). The myriad benefits due to exercise and physical activity in ESRD that translate to higher HRQoL are well reflected in observational and interventional studies. Kutner *et al.* (205) showed that in 226 dialysis patients, physical activity was associated with the most number of HRQoL measures compared to any other variables. Positive associations were found between physical activity and the HRQoL questionnaire SF-36 perceived physical functioning, overall PCS score, vitality, general health, mental health and social functioning domains (205).

Intervention studies that have prescribed AT (182, 206, 207), RT (68, 72, 76) or a combination of both (208-210) can improve some domains of HRQoL, particularly in the physical functioning domain and/or the PCS score of SF-36 (68, 72, 76, 209, 210). No research has compared and elucidated any differential effects of AT versus RT on self-reported HRQoL. Studies investigating isolated RT, however, have reported some positive findings. Cheema *et al.* (76) reported improved vitality in hemodialysis patients after high intensity RT while. Similarly, Chen *et al.* (72) reported their low-intensity strength training can improve self-reported physical functioning ($p=0.02$). Segura-Orti *et al.* (194) reported no change in HRQoL measured with SF-36 and this may be due to the low intensity of their exercise program, which consisted of 4 lower extremities exercises using a mixture of ankle weight, elastic bands, human resistance and isometric muscle contraction.

In a study that prescribed a combination of 30 minutes of cycling and 30 minutes of strengthening and flexibility exercises, the effects of the intervention on HRQoL were assessed with several methods including SF-36 questionnaire, Quality of Life Index (Spitzer Index) and Scale of Life Satisfaction (209). The mean score of Quality of Life Index significantly improved

by 38.4%, Life Satisfaction score improved by 18.3% and the PCS score of SF-36 improved by 9.9% (209). A study conducted by Molsted *et al.* (208) used five months of high intensity, combined AT plus RT twice a week and showed that SF-36 physical functioning, bodily pain and PCS score were improved. Similarly, van Vilstern *et al.* (183) prescribed 12 weeks of exercise consisting of pre-dialysis RT and intradialytic cycling and showed an improvement in patient vitality and general health. Apart from these studies, there is a lack of comparative research to determine whether RT has a distinctive benefits to HRQoL in relation to AT. Nevertheless, the evidence does show that RT with and without AT can improve objectively measured physical functioning and consequently HRQoL.

To date, there has been little investigation on the efficacy of RT on other clinically important psychological outcomes in patients with ESRD including mental health and depression. Depression is perceived as a common psychopathology and under recognised in patients with ESRD (211, 212). The Dialysis Outcome and Practice Patterns Study Program (DOPPS) analysed 12 countries' patients with ESRD and found a 13.9% prevalence rate of physician-diagnosed depression and 43% when using a Center for Epidemiologic Studies Depression (CES-D) scale cut-off of ≥ 10 (213). Depression symptoms are also strongly linked to many HRQoL measures (203, 214) and were shown by the DOPPS to be inversely associated with aerobic physical activity but not with muscle strength/flexibility activity (215). Neither AT nor RT have shown any effect on the mental component summary (MCS) score of SF-36 (68, 72, 76, 194). One RT trial that was conducted by Cheema *et al.* (76) assessed depression level using the Geriatric Depression Scale (GDS) but did not find any significant change in response to 12 weeks of intradialytic RT intervention.

The results from mixed intervention studies of AT plus RT have been equivocal. Ouzouni *et al.* (209) did not observe a change in the SF-36's MCS score; however, depression level

measured by Beck Depression Inventory decreased by 39.4% ($p<0.001$) and the number of depressed patients was reduced after their 10-month mixed AT plus RT intervention. In another mixed intervention, Oh-Park *et al.* (210) found significant improvements in the MCS scores of SF-36 after 3-month of 2-3 times per week AT plus RT intervention. Conversely, De Paul *et al.* (184) reported no change in SF-36's MCS score. Depression level measured by Standard Depression Scale was not significantly different in van Vilsteren's (183) mixed intervention study too. More studies are therefore necessary to assess the isolated and/or additive effect of RT on depression symptoms in patients with ESRD.

2.17 Conclusion

There is sufficient evidence to support the prescription of intradialytic RT to patients with ESRD to improve a range of health outcomes (20, 42, 61, 97). However, there has been no investigation of the efficacy of PRT for improving arterial stiffness in this cohort, and how this adaptation is associated with other physiological changes to cardiovascular health, including markers such as EPCs, CRP and lipids. The majority of research generated to date has focussed on the effects of intradialytic AT on arterial stiffness and other cardiovascular risk factors (20, 61). To better understand the role PRT can play in improving cardiovascular health of patients with ESRD, there is a need to elucidate the concurrent effects of PRT on arterial stiffness and associated physiological, functional and psychological outcome. In addition, there is a need to develop novel, customized resistance training equipment to enhance the delivery of PRT in the hemodialysis setting to elicit better health adaptations in patients and enable more seamless translation to standard clinical care.

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Chapter 3
General Methods

3.1 Study Design

This study utilised a within-subjects non-randomised crossover trial design. The trial compared the outcomes of an initial 12-week usual care control period to a 12-week intradialytic RT intervention period in a single group of patients with ESRD (Table 3.1). Primary and secondary outcome measures were assessed at baseline (week 0), after the control period (week 12) and after the intervention period (week 26).

Table 3.1. Phases of the study

Phase	Testing	Control period	Testing	Intervention period	Testing
Week	0	1 – 12	13	14 – 25	26

The duration of the intradialytic RT intervention (12 weeks) was considered appropriate as previous clinical trials prescribing 12 weeks of AT have been successful in eliciting a reduction in arterial stiffness of hemodialysis patients (1, 2). Moreover, studies of RT have been shown to induce positive physiological adaptations, including improvements in inflammation and muscle mass and quality after 12 weeks of training (3-5). The University of Western Sydney Human Research Ethics Committee (Research Code: H9651) and the Central Northern Adelaide Health Service (RAH Protocol No.: 120507) approved all research procedures. Written informed consent was obtained from all patients prior to study participation (Appendix 5). The trial was registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR: 12612000496819) upon receipt of ethics approval on the 8/05/2012.

3.2 Participants

3.2.1 Recruitment Sites

The participants were recruited from four dialysis centers in South Australia, including the Payneham Dialysis Center, the Wayville Satellite Dialysis Center, the Hartley Dialysis Center and the Queen Elizabeth Hospital's dialysis ward. All study procedures were completed within one dialysis center before proceeding to the next given that only the principal investigator was involved in the data collection (i.e. recruitment of participants, assessments, and delivery of the intervention).

3.2.2 Medical Screening

All patients regularly attending the dialysis centers for maintenance hemodialysis treatment (i.e. three sessions per week) were screened for eligibility. The screening process involved review of the medical and clinical records of the patient, clearance from the nephrologist of the patient (Appendix 3), and interview of the patient by the principal investigator. Eligibility criteria: (1) adult aged ≥ 40 years, (2) medically stable and adequately dialysed ($Kt/V \geq 1.2$) for greater than three months, (3) able to ambulate independently or with an assistive device for ≥ 50 m, (4) no limb amputation, (5) no acute or chronic medical condition that contraindicated or prevented the performance of RT during hemodialysis treatment, (6) cognition and English language sufficient to understand research procedures and provide written informed consent, (7) sedentary (i.e. less than 120 minutes of moderate intensity physical activity per week) (6), (8) no current participation in an exercise regimen involving RT.

3.2.3 Participant Recruitment

Hemodialysis patients are typically highly sedentary and reluctant to participate in exercise programs (7). Therefore, eligible participants were approached individually by the principal investigator (D.C.) in an attempt to build rapport by addressing any fears, concerns and queries about study participation. A video recording which promoted intradialytic exercise performance and perceptions of patients enrolled in existing exercise programs at the Hampstead Dialysis Unit in Adelaide were shown to patients during their dialysis sessions *via* a laptop computer (Available at: <https://www.dropbox.com/s/68s6o3zcwvndbsr/Dialysis%20Ex%20Promo-2012.m4v?dl=0>).

In addition, a participant information sheet (Appendix 4) was provided to patients to read, consider and discuss with their family members for a one-week period prior to re-approaching the participant regarding participation.

3.3 Outcome measures

3.3.1 Physiological Outcomes

3.3.1.1 Pulse wave velocity (PWV) and secondary haemodynamic outcomes

Participants were first instructed to fast from food and caffeinated drinks for a minimum of 4 hours prior to testing. The brachial and posterior tibialis arteries sites were palpated and marked. The height of brachial artery site and sternal notch were measured using a stadiometer and the distance from the base of the foot to posterior tibialis site was measured using a large bone caliper. From these measures, distance between brachial artery site to sternal notch and distance between posterior tibialis artery to sternal notch were calculated.

The following measurements were collected with participants in a supine position. Resting brachial blood pressures were evaluated after 15 min supine rest using an aneroid sphygmomanometer (1512 Riester Ri-san, Germany) and stethoscope. Three blood pressure measures were taken 1 minute apart with the average of two closest measures recorded. Applanation tonometry using the SphygmoCor System and Program (AtCor Medical Pty, Sydney, Australia) was then applied to measure the primary outcome PWV, and the augmentation index (AI).

A hand-held, high fidelity tonometer (Millar Instruments, Houston, Texas) was applied at the radial artery to measure the AI. The SphygmoCor algorithm also normalizes AI to a heart rate of 75 beats per minute since AI is affected by factors such as ejection fraction and heart rate (8). The SphygmoCor Program is able to derive aortic blood pressure parameters using a validated and reproducible generalised transfer function (9, 10). Pulse pressure was calculated by deducting the diastolic pressure from systolic pressure. To measure PWV, the tonometer was applied to the brachial artery and posterior tibialis artery that give clear waveforms. If there are differences between the positions of the tonometer to the palpated sites, the distances measured earlier were corrected according to the differences and entered into the SphygmoCor Program for PWV data collection. The SphygmoCor device has been used in three previous trials which investigated the effect of AT in patients receiving maintenance hemodialysis treatment for the management of ESRD (2, 11, 12). AI and PWV measured using the device is highly reproducible in this cohort (9). Due to fluid shifts unique to hemodialysis patients as a consequence of hypervolaemia and thrice weekly dialysis treatment, PWV and AI can fluctuate within a week (13). However, the affect of such fluid shifts on indices of arterial stiffness was minimised by conducting the measures on the same non-dialysis day of the week for the baseline and follow-up assessments (week 13 and 26) (9, 14). According to Di Iorio et al, this may be the

best approach to evaluate arterial stiffness over time in this patient population (13). Post intervention testing was completed at least 72 hours after the completion of the final exercise session to ensure that changes were independent of acute effects. The detailed procedure for conducting PWV and AI assessments is detailed in Appendix 6.

A total of 16 patients agreed to have their arterial stiffness measures assessed twice by the same investigator during baseline assessment to determine reliability. AI was not measured in 1 patient due to difficulty in detecting the patient’s radial arterial pulse. Duplicate measures of PWV measures were not collected from 4 patients due to difficulty in capturing clear pulse waveforms and lack of time. The reliability of the measures was determined based on coefficient of variability percentage (CV%) and intra-class correlation coefficient (ICC) of the arterial stiffness measures (i.e. PWV, AI and normalised AI) were established prior to the study (Table 3.2). The coefficient of variation percentage (CV%) was defined as the percentage of the standard deviation divided by the mean; the average CV% of the total cohort was reported. Table 3.3 showed the individual data of the repeated measures.

Table 3.2. Reliability of PWV and AI measures

Variable	Mean	CV%	ICC (Single measure)	ICC (Average measure)
PWV (<i>n</i> =12)	13.9	7.2	0.883	0.938
AI (<i>n</i> =16)	35.6	4.8	0.973	0.987
Normalised AI (<i>n</i> =12)	31.5	6.2	0.931	0.964

Table 3.3. Repeated measures of AI and PWV of participants

Participant ID	AI Measure 1	AI Measure 2	AI-75bpm Measure 1	AI-75bpm Measure 2	PWV Measure 1	PWV Measure 2
3	39	35	32	28		
4					14.5	15.6
6	19	16	16	12	9.2	10.8
7	46	45	36	34	17.5	16.9
8	20	21	19	20	10.2	11.4
9	26	24	28	25	11.3	11.2
11	44	43	42	41	14.9	15.8
12	49	47	40	37	12.3	15.5
14	33	37	29	31		
15	44	41	40	37		
16	48	50	34	37	20.8	22.1
19	35	35	36	38	10	11.2
23	22	27	23	28		
25	27	26	35	35	15.5	12.4
31	41	42	30	30	14.7	13.8
32	26	29	27	31		
33	51	51	37	39	12.3	13.4

AI-75bpm, Augmentation index normalised to 75 beats per minute. PWV is presented in ms^{-1} . AI and AI-75bpm is in percentage.

3.3.1.2 Haematological Outcomes

Endothelial progenitor cells (EPCs)

Peripheral blood samples were taken from each patient just prior to each participant's first hemodialysis session of week 0, week 13 and week 26. 20mls of blood was collected via venepuncture into 10ml lithium heparin coated Vacuette tubes (Greiner Bio-One, Kremsmuenster, Austria). Samples were diluted 1:1 with sterile phosphate buffered saline (PBS) and mononuclear cells (MNCs) were isolated via Lymphoprep™ (Axis-Shield, Oslo, Norway). Cells were washed two times in HUVE media (Media 199 (Sigma); containing 20% FCS

(Hyclone, Utah, USA), 1.5% sodium bicarbonate, 2% HEPES buffer solution, Penicillin Streptomycin, sodium pyruvate (all Gibco Invitrogen, Gaithersburg, MD, USA) and non-essential amino acids (Sigma) before flow cytometry staining.

MNCs were analysed for cell surface expression of various markers by flow cytometry. Cells were blocked with 10ul of human FcR blocking reagent (Miltenyi Biotec, Bergisch Gladbach, Germany) for 10 minutes. Cells were then incubated in 100 µl HUVE media with either mouse anti-human DSG2 (1 µg, Abcam, MA, USA) or mouse IgG1 isotype control (1µg, BD Bioscience) for 30 minutes on ice. Following a wash with HUVE media cells were incubated with goat anti mouse DyLight® 650 (1:100, Abcam) in 100 µl HUVE wash for 30 minutes on ice. The cells were blocked with 5ul normal mouse serum (Sigma-Aldrich, MO, USA)) then immediately incubated with panels of mouse anti-human conjugated antibodies; anti CD14 PE-Cy7, anti CD144 FITC, anti CD34 Percp-Cy5.5, anti CD45 Amcyan, anti CD31 V450 (all BD Biosciences) and anti-CD133-PE (Miltenyi Biotec) used as per manufacturers instructions for flow cytometry along with fixable viability dye eFlour®780 (1:1000, eBioscience, CA, USA) in a final volume of 80ul of HUVE media for 30 minutes on ice. The cells were then resuspended in FACS fix (1% formaldehyde, 20g/L glucose, 5mM sodium azide, made up in PBS) prior to analysis using a FACS Aria II (BD Biosciences) with FACS DIVA software (BD Biosciences). Further analysis was performed using FCS Express 4 Flow Cytometry: Research Edition (De Novo Software, CA, USA). The analysis of EPCs was performed by a research assistant in the Vascular Biology and Cell Trafficking Laboratory, Center for Cancer Biology, SA Pathology. Progenitor cells (CD133+CD34+) and endothelial progenitor cells (CD133+CD34+CD31+) are presented as percentage of MNCs.

C-Reactive Protein (CRP)

Blood samples for CRP assay were collected in lithium heparin coated Vacuette tubes by the dialysis nurses and collection was confirmed by the the principal investigator (D.C.). CRP assays were analysed using the Siemens Healthcare Diagnostics ADVIA Chemistry system (Tarrytown, New York, USA). The method to measure wide range CRP in serum and plasma by a latex-enhanced immunoturbidimetric assay was applied. This measure was based on the principle that the analyte concentration is a function of scattered light caused by the latex aggregates. The latex particles coated with anti-CRP rapidly agglutinating to CRP-forming aggregates. The CV% is 3.8 for a mean value of 6.8, and 5.9 for a mean value of 94.5.

Lipid Profile

Blood samples for blood lipid assays were collected in lithium heparin coated Vacuette tubes. Blood lipids were analysed using the Siemens Healthcare Diagnostics ADVIA Chemistry system (Tarrytown, New York, USA). An enzymatic method using cholesterol esterase, cholesterol oxidase conversion followed by a Trinder reaction was used to measure concentrated cholesterol. HDL-C cholesterol in serum and plasma was measured without prior separation. Cholesterol from non-HDL-C particles was released and eliminated in the first step of the reaction. Cholesterol in HDL particles was released in the second step by detergent in R2, and the HDL-C cholesterol was then measured by a Trinder reaction. The Triglycerides method was based on the Fossati three-step enzymatic reaction with a Trinder endpoint. The triglyceride was converted to glycerol and free fatty acids by lipase. The glycerol was then converted to glycerol-3-phosphate by glycerol kinase followed by its conversion by glycerol-3-phosphate-oxidase to hydrogen peroxide. A colored complex was formed from hydrogen peroxide, 4-aminophenazone and 4-chlorophenol under the catalytic influence of peroxidase. The absorbance of the complex

was measured as an endpoint reaction at 505/694 nm. The single-reagent procedure quantitates the total triglycerides including the mono and diglycerides and the free glycerol fractions.

The following equation was then used to calculate LDL cholesterol:

$$\text{LDL-C cholesterol} = (\text{Total Cholesterol} - (\text{Triglycerides}/2.2)) - \text{HDL-C cholesterol}$$

The CV% of the total cholesterol, HDL-C and triglyceride at two different mean concentrations is presented in Table 3.4 (CV=1.3-6.3%).

Table 3.4. The associated means and CV% of lipids

Lipid	Mean	CV	Mean	CV
Total cholesterol mmol/L	5.69	4.2	2.94	1.3
HDL-C mmol/L	1.1	4.8	0.31	6.3
Triglycerides mmol/L	2.43	4.2	1.09	3.7

3.3.1.3 Anthropometric measures

Weight and height were measured using a Taylor 5596A scale and a SECA portable stadiometer, respectively. Body Mass Index (BMI) was computed as the ratio of weight (kg) over height squared (m²). BMI > 25 kg/m² was categorised as ‘overweight’, while BMI > 30 kg/m² was categorised as ‘obesity’ (15). Waist circumference was measured using calibrated non-metallic tape, according to standard protocol (Appendix 9) (15).

3.3.2 Functional Outcomes

3.3.2.1 Upper body muscular strength

A Jamar™ dynamometer was used to measure handgrip strength of both arms. The measurement can be used to represent overall upper body muscle strength (16). The Jamar dynamometer, adjusted to its second most narrow hand position, was held by a seated subject. The participant had the shoulder adducted and in neutral rotation, the elbow flexed to 90 degree angle and the forearm and wrist in neutral. The participant was then instructed to grip as hard as possible for at least 3 seconds before relaxing. The participant had a 30s rest between each trial of each arm, with the best score recorded in kilograms for both the fistula-containing and non-fistula arms.

3.3.2.2 Lower body strength

Muscular strength was assessed using a single leg press. A three-repetition maximum (3RM; i.e. the heaviest weight lifted with proper technique for only three repetitions was performed according to standard strength testing protocols (17) using the Maxim™ dialysis weight machine. The 3RM for both the left and right leg were added to create a summary score for lower body muscular strength. The protocol for the 3RM test is detailed in Appendix 7.

3.3.2.3 Six minute walk test

The six minute walk test is a validated functional measure that reflects aerobic and functional capacity in older adults aged 60 – 80 years (18). The six-minute walk enables the assessment of a wide range of physical fitness levels including those who cannot run and thus the test is appropriate and commonly used in ESRD (18-20). Performance was determined by the

maximum distance walked in six minutes along a circuit. The protocol for the six-minute walk test is detailed in Appendix 8.

3.3.3 Psychological Outcomes

3.3.3.1 Geriatric Depression Scale

The GDS (Appendix 10) was used to evaluate depression symptoms with scores ranging from 0 to 30 categorised as: 'normal' (0 – 9), 'mild depression' (10-19), and severe depression (20-30) (21). GDS is found to be an internally consistent measure and correlates with the number of Research Diagnostic Criteria symptoms for depression (22) and thus is accepted as a reliable and valid self-rating depression screening scale for elderly populations. The GDS has also shown to have good internal reliability in adults younger than age 65 (23). The GDS is non-somatically focused, and can be easily administered by either an observer or the patient personally. In cognitively intact patients older than 65, the GDS is preferred over other depression screening instruments including the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale (24).

3.3.3.2 Health-related quality of life (HRQoL)

The SF-36 Version 1.0 was used to evaluate changes in eight domains of HRQoL, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health (25). In addition, the instrument provides scores for a PCS and a MCS calculated from the relevant HRQoL domains. The SF-36 is designed for self-administration and has demonstrated a high degree of internal consistency and construct validity (26). The SF-36 has been shown to be a valid tool to assess physical functioning in

ESRD (27) and sensitive enough to detect changes over time in response to resistance or aerobic exercise training intervention in dialysis patients (12, 28, 29).

3.4 Clinical Co-variates

The Physical Activity Scale for the Elderly (PASE) (Appendix 10) was used to evaluate and quantify leisure and daily activity level at week 0, week 13, and week 26 as a confounding variable (30). Additional factors potentially related to the adaptations under investigation were extracted during the recruitment and screening process and baseline testing by means of standard questionnaires and assessments, and were entered into analytic models as appropriate. These factors included demographic characteristics (i.e. age, gender, occupation, marital status, living arrangement, income, smoking history, alcohol intake, etc.), medication and supplement usage and dosage, adverse events related to medication/supplement intake, and history of medical and surgical procedures received (Appendix 10).

3.5 Changes in Health Status, Adverse Events and Compliance

Changes in health status occurring during the control and intervention periods was documented by means of a structured questionnaire of open-ended questions that was administered weekly, during dialysis treatment (Appendix 11). This questionnaire was designed to obtain information regarding acute illnesses, falls, changes in medication dose and usage, adverse events related to exercise participation and all visits to health care professionals. An adverse event was defined as any injury, impairment or medical condition that was directly or suspected to be due to performing the prescribed exercise. In addition, the clinical notes of each

patient were reviewed on a week basis to document any dialysis-related adverse events or complaints. Overall adherence to training was computed as the total number of exercise sessions attempted divided by the total number of exercise sessions offered, multiplied by 100%. In addition, the percentage of each of the 10 prescribed PRT exercises completed was computed as the total number of sets completed divided by the total number of sets prescribed, multiplied by 100%. Reasons for missing or non-attempt of exercise sessions were also documented.

3.6 Assessment protocol

As mentioned, all outcome measures were assessed at baseline (week 0), after the control period (week 13) and after the intervention period (week 26) (Table 2) in the dialysis centers participants received hemodialysis treatment. The testing was scheduled on the second or third non-dialysis day of the week. Assessments were completed in the following order: anthropometric measures (i.e. height, weight, waist circumference), supine blood pressure, arterial stiffness (i.e. PWV and AI), six-minute walk, muscular strength (i.e. maximal handgrip strength, three repetitions-maximum leg press). The testing session took approximately 1 to 1.5 hour to complete. Follow-up testing in week 26 was completed at least 48 hours after the last exercise session. Each assessment was conducted by the principal investigator (D.C.). The dialysis nurse collected bloods for haematological measures just prior to the patients' dialysis session at each timepoint and immediately forwarded and assayed by the haematology, biochemistry and vascular biology and cell trafficking laboratories of Institute of Medical and Veterinary Science. Bloods for EPCs assays were collected on the first dialysis day of the week while bloods for CRP and lipid profile were collected on the second dialysis day of the week.

Psychological outcome measures and PAL, evaluated using questionnaires (i.e. SF-36, GDS and PASE) were self-administered by participants within their own home after instructions were provided by the principal investigator. The questionnaires were collected and checked by the principal investigator to ensure they were completed correctly.

3.7 Control period

During the control period (week 1 – 12), participants were provided usual medical and dialysis care but were given no instructions to exercise or access to equipment.

3.8 Intervention period

The RT intervention is fully detailed in Appendix 12. Six upper-body and four lower-body exercises were prescribed in each dialysis session (3 sessions per week). Upper body exercises were comprised of shoulder press, chest press, seated row, biceps curl and triceps extension and seated back extension. Lower body exercises were comprised of leg press, knee flexion, knee extension, supine bent knee hip flexion or leg raise depending on participant's ability (Figure 3.1). Table 3.5 shows the equipment that was used to perform each exercise.

Table 3.5. Equipment used for each exercise prescribed

Equipment	Exercises
Customized weight machine	Chest press, Seated row Leg press, Knee flexion Supine bent knee hip flexion/leg raise
Free weights (dumbbells)	Shoulder press Bicep curl Tricep extension
Elastic tubings	Back extension Knee extension Supine bent knee hip flexion/leg raise

Table 3.6. Progression of the resistance training programme

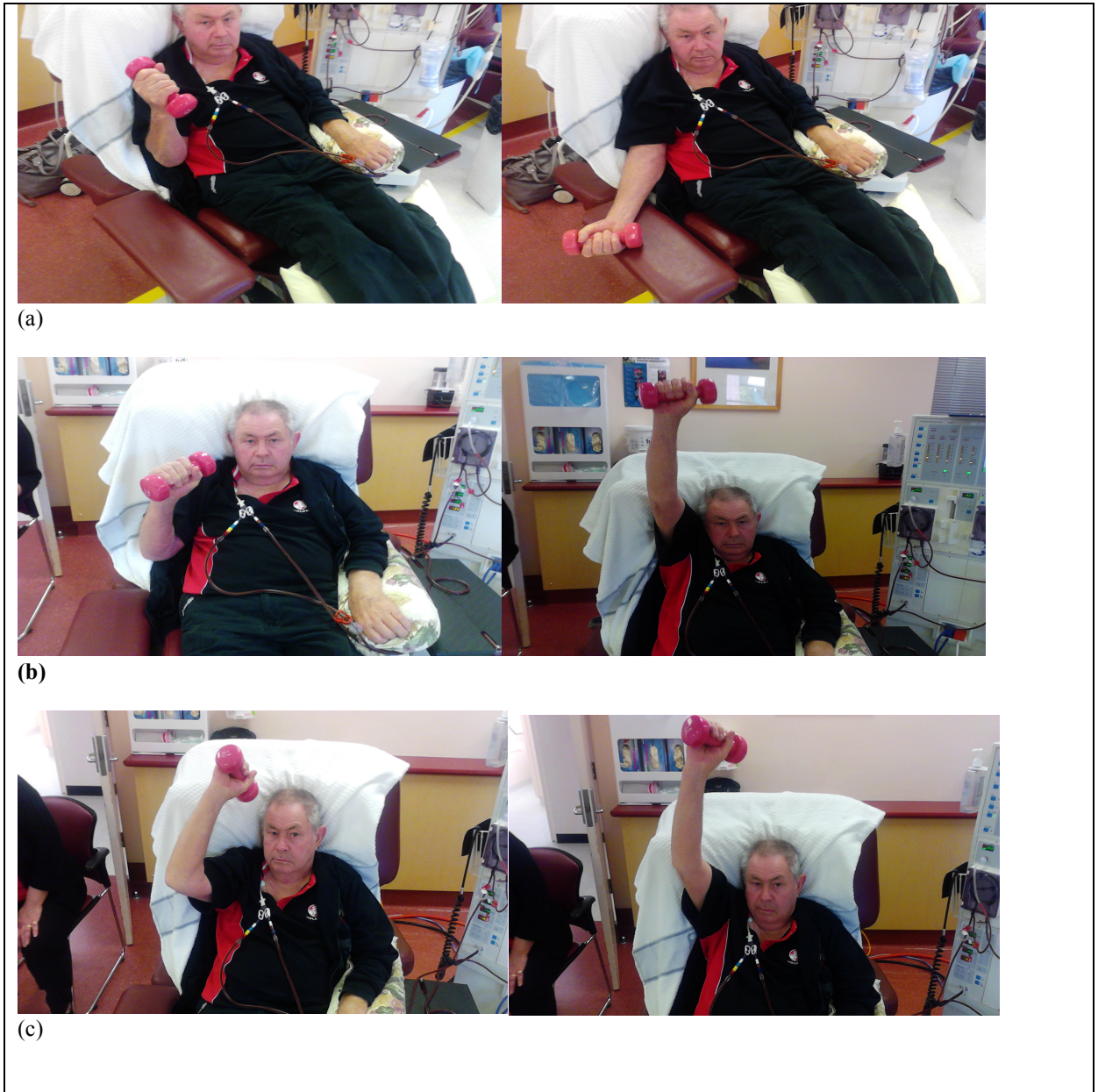
Week	Number of sets	Number of repetitions	RPE
1 – 2	3	12 – 15	12 – 13
3 – 4	3	12 – 15	13 – 14
5 – 12	3 – 4	10 – 12	14 – 15

RPE, rating of perceived exertion

During the intervention period, the participants were prescribed light-to-moderate intensity RT three times per week during their routine hemodialysis sessions. The principal investigator aimed to have each participant complete their exercises during the first half of their dialysis session to avoid any risk of dialysis-induced hypotension. The principal investigator guided each participants in increasing the intensity (load) and volume (number of sets) of resistance training with strength adaptation. The rating of perceived exertion of each set was assessed using the Borg scale (15) (Appendix 13), and progressed according to Table 3.6. An exercise log sheet was used to track the progress of each participant (Appendix 14). The average duration of the exercise program was approximately 30 minutes; the efficiency of training was enhanced by having participants alternate exercises that use different muscle groups.

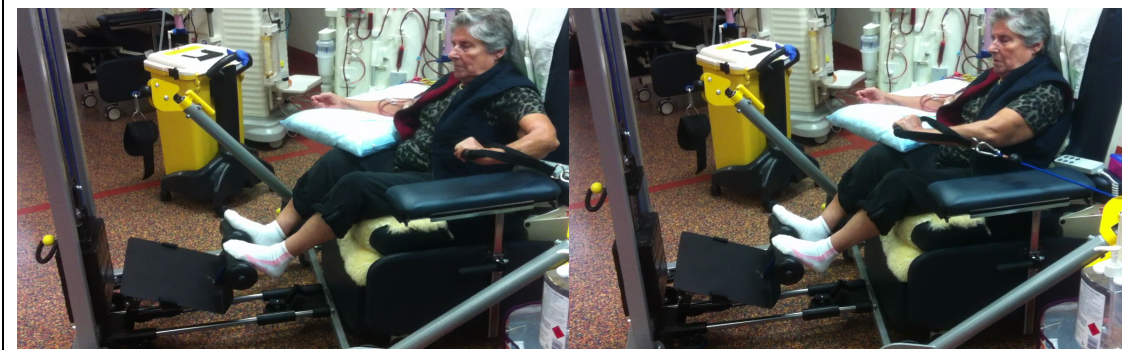
Figure 3.1. Specific resistance training exercises

(a) biceps curl with dumbbell, (b) shoulder press with dumbbell, (c) triceps extension with dumbbell, (d) seated row with machine, (e) chest press with machine, (f) seated back extension with elastic tubings, (g) leg press with machine, (h) knee flexion with machine, (i) knee extension with elastic tubings, (j) supine bent knee hip flexion with machine





(d)



(e)



(f)



(g)



(h)



(i)



(j)

The exercise program was designed to be performed with the patient in a seated or supine position receiving dialysis. A combination of RT equipment was used to optimally target all major muscle groups of the body. The equipment included a novel Maxim Fitness™ (Hindmarsh, SA, Australia) exercise device (see section 3.9), Thera-band™ elastic tubing (Akron, Ohio, USA) with handles (Practitioner Supplies, Clovelly Park, SA, Australia) and free weight dumbbells (Celsius™, China). As the elastic tubings have up to 5 colour graded resistance, progression in resistance was attained by connecting different colours of tubing to handles. A guide to the progression of elastic resistance has been developed by the principal investigator (31). Standard hemodialysis chairs (Fresenius Medical Care, Scoresby, Victoria, Australia) were used during the training sessions. The upper limb containing the vascular access was exercised 10 - 15 minutes prior to each dialysis session in the patient waiting area. Patients with a vascular catheter access were instructed to perform all the exercises during their dialysis session, unless they refused.

3.9 Prototype design and development

The lead author (D.C.) developed the novel exercise device prototype in consultation with Maxim Strength Fitness Equipment Pty. [www.maximfitness.net, Hindmarsh, SA, Australia (Figure 3.2)]. The lead author is an accredited exercise physiologist¹⁷ who has worked for over six years prescribing exercise as standard care in dialysis centers in the Adelaide metropolitan area. In clinical practice, the lead author routinely utilized a custom-designed resistance training device (Maxim Strength Fitness Equipment Pty., Adelaide, Australia) developed and tested by Bennett et al (32). The device (32) consisted of a weight-adjustable, pulley system that applied resistance (up to 32 kg) to the lower body musculature in three movements: leg press (target

muscles: quadriceps, gluteal, hamstrings and calves), knee flexion (target muscles: hamstrings) and knee extension (target muscles: quadriceps). The prototype designed in the present study advanced upon this initial design (32) by enabling the performance of both upper and lower body exercises during dialysis with heavier loads.

The lead author first conceptualized and sketched an equipment design that could provide an overload stimulus to all of the major muscle groups, while considering the space available in participating dialysis centers and the dimensions of standard hemodialysis chairs (Fresenius Medical Care, Scoresby, Victoria, Australia). Portability and functionality were considered as key aspects of the design; i.e. the device would require wheels with a braking mechanism allowing for safe positioning during pre-dialysis training (of the fistula containing arm in the patient waiting area) and intradialytic exercise training, and need to be stowed when not in use. Further, the PRT exercises needed to be administered without complicated set-ups or configuration changes, easily used in practice by both exercise physiologists and/or dialysis nursing staff. The concept of a portable device including wheels and brakes was adopted from Bennett et al. (32) This design was finalized after several discussions with the production manager of Maxim FitnessTM to ensure its feasibility and the mechanics to allow bilateral or unilateral movement. As the device was first of its kind, the process of designing and developing it took approximately 4 months.

The structure was made of steel and measured 1.16 m wide, 0.94 m long and 1.61 m tall. The design consisted of a trapezium-shaped base, with two lever arms pivoting from the corners of the widest side and the pin-loaded weight stack is positioned on the shorter side (Figure 3.2). The lever arms allowed the performance of resistance exercises involving pushing (e.g. chest press) and pulling (e.g. seated row, hip flexion) while a plate attachment was connected to a pair of steel cables enabling leg press and knee flexion exercises. All exercises performed with the

device are presented in Table 1. Loading of each exercise ranged from 2.5kg to 59kg; the weights were pin-loaded and easily adjusted by the supervising exercise physiologist or nurse. 1kg add-on weights are available for gradual increment (Figure 3.2).

Figure 3.2. Customized weight machine



(a) Front view



(b) Rear-side view



(c) Pin-loaded weights

3.10 Statistical Analyses

Analyses were performed using the Statistical Package for the Social Sciences (IBM©, SPSS Version 19.0). All available data were included regardless of patient compliance to the intervention. All data were inspected visually and statistically for normality at each timepoint (weeks 0, 13, and 26). Normally distributed data were described using mean \pm standard deviation. Non-normally distributed data were log-transformed across the three timepoints prior to entry into parametric statistical models. Primary analysis incorporated a linear mixed model defining individual as the random effect with the outcome measure evaluated across three timepoints (weeks 0, 13, 26). Each model was also adjusted for age, gender, hemodialysis vintage, and interactions for time by age, time by gender and time by hemodialysis vintage. P-values were reported for the change from week 0 to week 13 and change from week 13 to 26. In addition, the mean difference and effect size were computed comparing the control period (week 13 – week 0) to the intervention period (week 26 – week 13).

There are no published data on the effects of RT during hemodialysis on arterial stiffness in patients with ESRD. The sample size estimate was therefore determined by a post hoc sample size computation provided by Koh *et al.* (12) following the completion of a recent RCT comparing intradialytic aerobic exercise training to home-based aerobic exercise training and to usual care control in a cohort of patients with ESRD. The data collected by Koh *et al.* (12) suggested that 36 patients per group would be needed to detect a -1.0 m/s statistically significant and clinically meaningful change in PWV between the exercise and the control group in a parallel arm randomised controlled trial (ES = 0.67; α = 0.05 and $1-\beta$ = 80%). Replacing the parallel groups design with a cross-over and assuming between measures correlation of 0.5, the

required sample size was computed as $n=20$ to detect the same effect size on this outcome measure.

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Chapter 4

Resistance Training In End Stage Renal Disease: Systematic Review And Clinical Trial Recommendations

4.1 Abstract

Background: This systematic review provides an overview of the extant literature on progressive resistance training (PRT) in patients with ESRD and outlines recommendations for future trials.

Methods: A non-meta-analytic, systematic review of all published literature evaluating the chronic (>6week) application of PRT in patients with ESRD using electronic databases.

Results: The search yielded 16 clinical trials, including 11 randomized controlled trials (RCT), four uncontrolled trials and one trial involving a within-subjects control period plus RCT. RCT quality ranged from low (4/10) to high (10/10) with a mean quality score of 7.3/10; 7/11 RCT had a quality score ≥ 7.5 . All trials evaluated chronic adaptation to PRT across a range of important outcomes. The evidence suggests that PRT can induce muscle hypertrophy, and improve aspects of physical functioning and health-related quality of life (HRQoL) in this population. There is also preliminary evidence to suggest that PRT may reduce protein-energy malnutrition and cardiovascular risk factors, including CRP, total cholesterol, triglyceride, and measures of insulin resistance in patients with or at-risk of comorbid type 2 diabetes. The evidence base for PRT adapting some of the endpoints investigated to date remains inconsistent (e.g. physical performance tests, obesity outcomes), and many other pertinent clinical outcomes remain to be investigated.

Conclusion: RCT are required to investigate a range of novel research questions related to the benefits and application of PRT in this cohort and its patient subgroups (e.g. diabetes, depression, dyslipidemia, etc.). Future studies must be of high methodological quality to inform clinical practice guidelines.

4.2 Introduction

The global incidence of end-stage renal disease (ESRD) continues to rise annually (1). Accompanying this rise is growth of the prevalent hemodialysis population (1). These trends are being driven by an unprecedented burden of hypokinetic, non-communicable diseases, and particularly the type 2 diabetes-obesity pandemic (2). As the ESRD patient population continues to grow, greater efforts must be directed toward improving patient outcomes in this cohort, including morbidity, mortality and health-related quality of life (HRQoL).

Progressive resistance training (PRT) is an anabolic form of exercise that involves challenging the skeletal muscles with unaccustomed loads, usually in the form of free- or machine weights. Clinical trials in other cohorts have consistently shown that chronic RT interventions (>6 weeks) can counteract many impairments that accrue as a consequence of ageing and hypokinetic diseases (3). PRT is a modality of choice for inducing skeletal muscle hypertrophy and enhancing bone mineral density (4, 5). These adaptations often underlie improvements in physical functioning (e.g. muscular strength), activities of daily living (6-8) and HRQoL (9-11). Accumulating evidence also suggests that PRT can induce cardiovascular system adaptation, including the improvement of cardiovascular disease (CVD) risk factors (e.g. hypertension, blood lipids, visceral fat, insulin resistance, glycemic control and circulating c-reactive protein (CRP)) (12-16). The many potential benefits of PRT might be particularly important for patients with ESRD who suffer from various physiological, functional and psychological impairments, contributing to poor HRQoL (17), low physical activity and fitness, and high CVD-related and all-cause mortality (18).

In 2002, Headley et al (19) conducted the first study of isolated PRT in patients with ESRD. Ten hemodialysis patients were prescribed 12 weeks of PRT during non-dialysis time. Each training session consisted of 9 machine-weight exercises targeting all major muscle groups.

Participants significantly improved several measures of physical functioning, including six-minute walk, maximal walking speed, sit-to-stand movement time and leg extension strength from pre to post training. Since this initial study (19), numerous investigations have shown that chronic PRT (>6 weeks) prescribed within or outside of routine hemodialysis treatment is safe, and can induce clinically important adaptations in patients with ESRD (20-22).

Despite an accumulating evidence base, PRT and exercise training in general are not routinely prescribed in clinical practice to enhance health outcomes in this cohort. Therefore, the purpose of the present systematic review to provide an overview of the extant literature on PRT in patients with ESRD, and to outline recommendations for robust randomized controlled trials (RCT) to investigate a range of novel research questions related to the benefits and application of PRT in this cohort.

4.3 Methods

Search Strategy

A search of all published literature using the following electronic databases was conducted in August 2015: MEDLINE (OvidSP, Wolters Kluwer), PubMed (NCBI, U.S. National Library of Medicine), ScienceDirect (SciVerse, Elsevier), SPORTDiscus (EBSCOhost, EBSCO), Scopus (SciVerse, Elsevier), Web of Science (Web of Knowledge, Thomson Reuters), the Cochrane Library (John Wiley & Sons), Embase (OvidSP, Wolters Kluwer), CINAHL, and Google Scholar. Search syntaxes were developed in consultation with an experienced university librarian taking into account a broad range of terms and phrases used in definitions related to hemodialysis (e.g. chronic kidney disease, hemodialysis, end-stage renal disease, etc.) and PRT

(e.g. resistance training, resistance exercise, weight training, weight lifting, strength training, etc.). Reference lists of retrieved full-text articles were examined to identify additional articles not found by our search.

Study selection

A systematic, critical review was undertaken to overview the literature and guides the development of future RCT. The evidence base for PRT adapting many clinically important outcomes in this cohort is currently preliminary, and therefore a meta-analytic approach was not warranted. There were also important findings to convey from several uncontrolled trials. Therefore, randomized controlled trials (RCT), controlled trials, cross-over trials and uncontrolled trials that investigated the independent effect of PRT in adults with ESRD were included. Studies that did not evaluate the isolated effect of PRT within and/or between groups were excluded. PRT interventions included any form of loaded exercise using body weight (calisthenics), equipment (machine weights, free weights) or apparatus (elastic bands), prescribed during or outside of hemodialysis treatment with the potential to increase muscular strength. The interventions had to be at least six weeks in duration. Trials prescribing PRT with additional neuromuscular, weight-bearing activity (e.g. balance training) were included, while those prescribing PRT interventions combined with aerobic training, or prescribing repetitive hand-grip (e.g. ball squeezing) exercise only, were excluded. Outcomes that were potentially responsive to PRT based on the evidence in apparently healthy or other chronically diseased cohorts, were included. Citations were compiled in an Endnote X7© (Thomson Reuters) file and duplicates were identified and deleted. Both authors independently reviewed the titles and abstracts of each

reference for potential inclusion. Each reviewer then performed a second screening on the full text version of these articles; disagreements were resolved by discussion.

Quality assessment

A quality checklist was designed based on established criteria for the assessment of RCT and was extended for the critique of other study designs as appropriate (23, 24). Quality items reviewed, each worth 1.0 numerical point, were as follows: (1) evidence of randomization and concealment of treatment allocation, (2) statistical similarity of groups at baseline, (3) specification of eligibility criteria, (4) blinding of outcomes assessors, (5) reporting of compliance, (6) supervision of exercise sessions, (7) reporting of dropouts, (8) presenting data for primary and secondary outcomes, (9) use of intention-to-treat analysis, and (10) reporting of adverse events. Summed scores to range from 0 to 10 points with higher scores reflecting better quality.

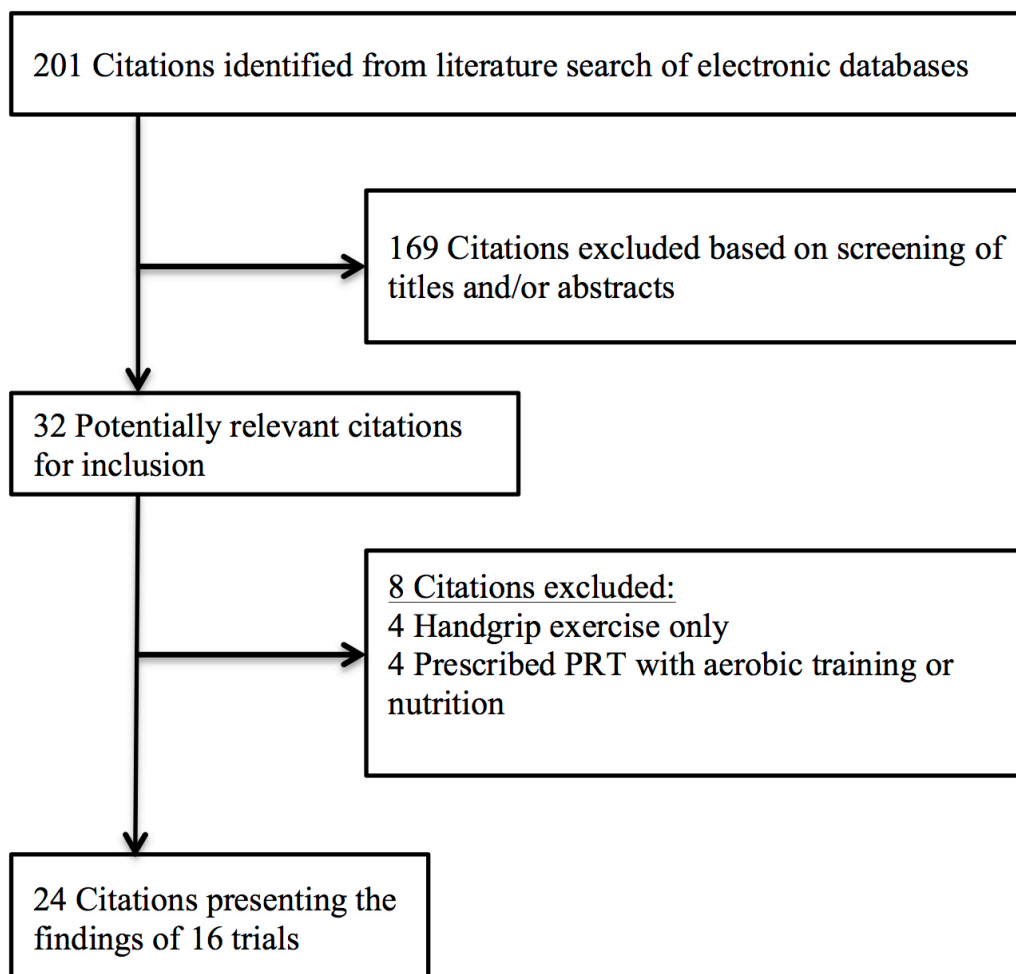
Data extraction

The following data were extracted using a standard proforma: study design, study population characteristics (inclusion/exclusion criteria), group(s) and sample size, PRT intervention (e.g. specific exercises, number of sets per exercise, number of repetitions per set, intensity (load), frequency and duration of training), selected outcome measures, and key findings.

4.4 Results

Figure 4.1 presents a flowchart summarizing identification of potentially relevant studies, and those included. Our search identified 201 citations after duplicates were removed. Of these, 168 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria. After further assessment of the remaining 33 citations, 8 were excluded for reasons listed in Figure 4.1, leaving 24 citations presenting the findings of 16 trials. A summary of these studies is presented in Table 4.1.

Figure 4.1. Flowchart summarizing identification of studies for review



Descriptive data synthesis

Of the 16 trials, 11 were RCT (25-36), four were single treatment group uncontrolled trials (19, 37-41) and one trial by Molsted and colleagues involved both a within-subjects control period and an RCT comparing PRT + protein drink to PRT + placebo drink (42-46).

The studies were published between 2002 and 2014. Five studies were conducted in the USA, four in Europe (i.e. Greece, Switzerland, Denmark, and Wales), three in Brazil, two in Asia (Iran, South Korea) and two in Australia. All studies enrolled exclusively maintenance hemodialysis patients with the exception of one study that also enrolled five peritoneal dialysis patients (42-46). In general, studies included patients who were adequately dialyzed ($Kt/V > 1.2$) and/or had received hemodialysis treatment for more than three months (26). Major exclusion criteria included uncontrolled cardiovascular diseases and other conditions that would physically limit or contraindicate participation in PRT. Sample sizes ranged from $n=10$ to $n=79$. The mean age of participants ranged from 42.8 to 70 years. All trials were open to both men and women; however, two studies recruited no women (28, 31), and one article published by Molsted et al (43) was limited to a subgroup of men only.

Table 4.1. Summary of studies prescribing progressive resistance training in patients with end stage renal disease

Study Identification	Inclusion/exclusion criteria	PRT Comparison Group(s) (n)	PRT Intervention	Selected Outcome Measures	Key Findings	Quality Score
<i>Randomized controlled trials</i>						
Kirkman <i>et al.</i> , 2014 Wales	Inclusion criteria: ESRD receiving HD three times per week. Exclusion criteria: Age <18 years, <3 months of HD, required support for ambulation, hemoglobin <11 g/dL, neuromuscular or catabolic conditions, anabolic treatment in previous 3 mo., uncontrolled medical condition	PRT (n=9) Placebo control (n=10)	Intradialytic: leg press utilizing resistance bands, loading up to 200 kg. 3 sets x 8-10 reps, 80% predicted 1RM (based on 5RM), 3x/wk, 12 wk	- muscle volume (thigh, <i>via</i> MRI) - physical functioning: knee extension strength, STS-30s, 8ft 'get-up-and-go', 6-min walk - HRQoL: 8 domains	↑ muscle volume ↑ knee extensor strength no Δ in any other outcome	8
de Lima <i>et al.</i> , 2013 Brazil	Inclusion criteria: 18-75 yr; HD three times per week, sedentary. Exclusion criteria: uncontrolled hypertension, cardiomyopathy, amputation, deep vein thrombosis, pallor, severe dyspnea, femoral fistula, arrhythmias, precordial pain, orthopedic, neurological or cognitive condition	PRT (n=11) Aerobic (n=10) Control (n=11)	Intradialytic: knee flexion and extension, and hip and knee flexion with foot dorsiflexion using weighted ankle cuffs, 3 sets x 15 reps, 40% 1RM, 3x/wk, 8 wk	- sub-maximal exercise capacity (4 min step test) - HRQoL: 11 domains	<u>In the PRT group over time:</u> ↑ step test (number of steps achieved) ↑ HRQoL in 3 domains (social support, patient satisfaction, and general health) no Δ in any other outcome	5.5

Song <i>et al.</i> , 2012 South Korea	Inclusion criteria: Age >18 yr; HD >3mo.; permission of nephrologist; ability to maintain a seated position; independent ambulation with or without an assistive device; adequate dialysis (Kt/V=1.2); stable during dialysis	PRT (n=20) Control (n=20)	Prior to each HD session: 6 upper body exercises using elastic bands, and 6 lower body exercises using sandbags, 3 sets x 10-15 reps, RPE 11-15, 3x/wk, 12 wk	- body composition: muscle mass, body fat and visceral fat area (<i>via</i> bioelectrical impedance), waist circumference, arm circumference - physical functioning: handgrip and leg strength, sit ups, sit and reach test, shoulder flexibility, single-leg balance - HRQoL: physical and mental component scales - blood lipids: TC, triglycerides, HDL-C, LDL-C	↑ in muscle mass ↑ leg strength ↑ HRQoL physical and mental component scales; ↓ body fat percentage ↓ total cholesterol and triglycerides no Δ in any other outcome	8
Orcy <i>et al.</i> 2012 Brazil	Inclusion criteria: HD >3mo, receiving EPO, Hb >9.0 g/dL, independent ambulation. Exclusion criteria: symptomatic ischaemic heart disease, myocardial infarction in previous 6 mo., uncontrolled hypertension, pleural or pericardial friction rub, aortic stenosis, musculoskeletal problem of the legs, vertebral fractures, participating in an exercise program	PRT (n=13) PRT + Aerobic (n=13)	Intradialytic: muscles groups targeted included: elbow/shoulder flexors, hip flexors with knees flexed/extended, and hip abductors. Equipment: elastic bands, dumbbells, balls and ankle weights of 1- 2 lbs, 3-4 sets x 10-15 reps, 3x/wk, 10 wk	- 6-min walk	no Δ in 6-min walk	10

Dong <i>et al.</i> , 2011 USA	Inclusion criteria: Age >18 yr; HD >3 mo.; adequate dialysis (Kt/V >1.2). Exclusion criteria: active inflammatory or infectious disease, pregnancy, hospitalization within previous 1 mo., cardiovascular disease and/or osteoarthritis and unable to exercise	PRT + Nutritional supplement (n=10) Nutritional supplement only (n=12)	PRT prior to each HD session: leg press using pneumatic equipment, 3 sets x 12 reps, 70% 1RM. 1RM tested at month 3 for load adjustment, 3x/wk, 6 mo.	- body mass - body composition: fat mass, body fat percentage, fat-free mass and leg fat-free mass (<i>via</i> DEXA) - albumin, prealbumin - CRP - leg strength (1RM)	no Δ in any outcome	6.5
Chen <i>et al.</i> , 2010 USA	Inclusion criteria: Age \geq 30 year; serum albumin <4.2 g/dl and HD 3x/week for >3 mo. with \geq 80% compliance. Exclusion criteria: Any unstable chronic condition, cardiac surgery, retina laser therapy, myocardial infarction, joint replacement or lower extremity fracture in previous 6 mo., severe cognitive impairment, leg amputation, current strength training	PRT (n=22) Placebo control (n=22)	Intradialytic: knee extension, dorsi/plantar flexion, leg curl, inner leg raises, dorsi/plantar flexion with straight legs using weighted ankle cuffs. First 8 sessions with no loading (RPE 2-4/10) progressed to 1-2 sets x 8 reps, RPE 6/10, 2x/week, 48 sessions	- physical functioning: STS-5x, 4m gait speed, balance tests, knee extension strength - body composition: body fat percentage, fat-free mass, leg fat-free mass (<i>via</i> DEXA) - HRQoL: physical and mental component scales - self-reported physical activity - self-reported ADL disability	\downarrow STS-5x \downarrow ADL disability \uparrow knee extension strength, \uparrow fat-free and leg fat-free mass \downarrow body fat \uparrow HRQoL physical component scale \uparrow physical activity level no Δ in balance and gait speed tests	8
Afshar <i>et al.</i> , 2010 Iran	Inclusion criteria: Age >20 yr; HD >3mo., no lower body dialysis graft. Exclusion criteria: infection, inflammation, autoimmune disorder, malignancy, severe muscle weakness or skeletal deformity,	PRT (n=7) Aerobic (n=7) Control (n=7)	Intradialytic: knee extension/flexion, hip abduction/flexion using ankle cuffs; 60% of 3RM, 2 sets x 8 reps. Sets increased to 3, as tolerated,	- BMI - blood lipids: TC, triglycerides, HDL-C, LDL-C - CRP	\downarrow CRP no Δ in any other outcome	4

	history of hypoglycaemia, cardiopulmonary contraindication to PRT (e.g. MI/CVA within prior 6 mo., angina, congestive heart failure), hospitalization in previous month, prior regular exercise training		3x/wk, 8 wk			
Segura-Orti <i>et al.</i> , 2009 Greece	Inclusion criteria: HD >3mo. and medically stable. Exclusion criteria: MI within previous 6 wk, uncontrolled hypertension, malignant arrhythmias, unstable angina, any disorder exacerbated by activity.	PRT (n=17) Placebo control (n=8)	Intradialytic: knee extension, hip/knee/ankle extension using ankle cuffs, 3 sets x 15 reps, hip/knee/ankle extension using elastic band, 1 set x 15 reps; isometric leg contraction (up to 6s), 1 set x 15 reps, 3x/wk, 24 wk	- physical functioning: STS-10x, STS-60s, 6-min walk, knee extension strength, graded exercise test in METS - HRQoL: physical and mental component scales	7.5	<p><u>Between groups:</u></p> <p>↑ right knee extension strength</p> <p>no Δ in any other outcome between groups</p> <p><u>Within PRT group:</u></p> <p>↑ STS60s</p> <p>↓ STS-10x</p> <p>↑ 6-min walk</p> <p>↑ GXT (METS)</p> <p>no Δ in any other outcome within PRT group</p>

Cheema <i>et al.</i> , 2007(a,b), 2011 Australia	Inclusion criteria: Age >18 yr, HD >3 mo., independent ambulation, Kt/V ≥ 1.2, stable on dialysis, ability to provide informed consent, cognition of English. Exclusion criteria: acute or chronic medical conditions that would preclude PRT or collection of outcome measures	PRT (n=24) Waitlist control (n=25)	Intradialytic: shoulder press, side shoulder raise, triceps extension, biceps curl, external rotation using weighted dumbbells; knee extension, hip flexion, hip abduction, straight-legged raise using weighted ankle cuffs, hamstring curl using elastic tubing; bilateral leg raises with no load performed seated or supine, 2 sets x 10 reps, RPE 15-17, 3x/wk, outcomes assessed at 12 wk and 24 wk	- muscle area and attenuation (thigh, <i>via</i> CT) - anthropometric measures: mid-arm and thigh circumferences, BMI, body mass - physical functioning: total strength (knee extension, hip abduction, triceps extension), 6-min walk - cytokines: CRP, TNF α , IL-1b, IL-6, IL-8, IL-10, IL-12 - HRQoL: physical functioning and vitality domains - depression - self-reported physical activity	<u>After 12 weeks in PRT vs. control:</u> ↑ muscle attenuation (↓ muscle lipid) ↑ BMI, body mass, arm and thigh circumferences ↑ total strength ↑ HRQoL (Physical Functioning and Vitality) ↓ CRP no Δ in any other outcome	9.5
Kopple <i>et al.</i> , 2007 USA	Inclusion criteria: stable hemodialysis patients, HD >6 mo, 25-65 yr, sedentary. Exclusion criteria: Hospitalization or systemic infection in previous 3 mo., active cancer; severe heart, lung, or liver disease, uncontrolled hypertension, inflammatory disease, insulin-dependent diabetes, severe osteoporosis, neuropathy, or musculoskeletal disease, leg	PRT (n=15) Aerobic (n=10) PRT + Aerobic (n=12)	PRT prior to each HD treatment: knee extension and flexion, leg press, calf extension using lower body machine. Wk 1-4: 1 set x 12-15 reps at 70% 5RM, Wk 5-8: 2 sets x 12-15 reps, Wk 8+: 3 sets x 6-8 reps at 80% 5RM, 3x/wk, ~21 wk	- anabolic and catabolic gene expression (mRNA and protein <i>via</i> muscle biopsy) - body mass, BMI - body composition: body fat percentage, fat-free mass (<i>via</i> DEXA) - cytokines: CRP, TNF- α , IL-6, dietary protein and energy intake	↑ muscle mRNA IGF-IEa ↑ IGF-I protein. no Δ in any other outcome	5.5

amputation, joint infirmity

Control (n=14)

Johansen <i>et al</i> , 2006 USA	Inclusion criteria: $Kt/V \geq 1.2$ and compliant with HD treatment. Exclusion criteria: Hemodialysis <3 mo.; catabolic state (e.g. HIV with opportunistic infection, malignancy, or infection requiring intravenous antibiotics over prior 2 mo., active intravenous drug use, thigh graft, contraindications to PRT	PRT (n=20) Nandrolone decanoate (n=19) PRT + Nandrolone decanoate (n=20) Placebo injection (n=20)	Intradialytic: knee extension, hip abduction and flexion, ankle dorsiflexion and plantarflexion using weighted ankle cuffs, 2–3 sets x 10 reps, 60% 3RM, weights increased when patient could perform 3 sets x 10 reps, 3x/wk, 12 wk	- body mass - body composition: fat-free mass, fat mass (<i>via</i> DEXA) - quadriceps muscle area (<i>via</i> MRI) - physical functioning: muscular strength (dynamic 3RM knee extension, hip abduction, hip flexion, isokinetic knee extension at 90 and 120 degrees/s, gait speed, STS-5x, stair climb) - HRQoL: physical functioning - physical activity (self-report and accelerometer) - profile of mood states (anger, fatigue)	↑ fat mass ↑ quadriceps muscle CSA, ↑ muscular strength (knee extension, hip abduction strength, hip flexion) ↑ HRQoL (physical functioning) trend toward ↓ fatigue (p=0.06) no Δ in any other outcome	8
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Within subjects + randomized controlled trial

Molsted <i>et al.</i> , 2013(a,b,c) 2014 (a,b) Denmark	Inclusion criteria: Age >18 years, >3mo. HD or PD, able to participate in the training program. Exclusion criteria: severe diabetic retinopathy, leg amputation, severe peripheral polyneuropathy, dementia, inability to speak Danish, and participation in conflicting trials	PRT+protein drink (n=13) PRT+non-protein drink (n=16)	Non-dialysis time: leg press, leg extension, leg curl using machine weights. Intensity increased from 15RM to 6RM over time, 5 sets per exercise, 3x/wk, 16 wk	<ul style="list-style-type: none"> - muscle composition (via muscle biopsy), - body mass, BMI - insulin resistance: OGTT, Matsuda ISI, HOMA2 - cytokines: CRP, IL-6 - anabolic hormones in men only: testosterone, luteinizing hormone, follicle stimulating hormone, estradiol, IGF-1, IGF-binding protein, sex hormone binding globulin - physical functioning: knee extension strength and power (rate of force development), STS-5x, STS-30s - HRQoL: 8 domains and 2 summary scales 	<p style="text-align: right;">9.5</p> <ul style="list-style-type: none"> ↑ Type 2x muscle fiber CSA and ↓ proportion ↑ body mass ↑ HRQoL domains (physical functioning, bodily pain, role emotional, mental health) and physical component summary scale ↑ knee extension strength and power ↑ STS-30s and EMG amplitude and RFD ↓ STS-5x ↓ insulin concentrations (fasting, 2hr of OGTT and total insulin area under the curve) in patients with T2DM or impaired glucose no Δ in any other outcome
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Uncontrolled trials

Moraes <i>et al.</i> , 2014 (a,b) Brazil	Inclusion criteria: Age >18 years >6 mo. HD. Exclusion criteria: autoimmune diseases, cancer, AIDS, amputated limb, bariatric surgery, regular exercise, taking catabolizing drugs, and catheter access for HD	PRT (n=37)	Intradialytic: Knee extension, thigh-knee-ankle flexion/extension, isometric leg extension, hip flexion with knee extended, 4 sets of 10 repetitions at 60-70% 1RM using elastic tubing, 3x/wk, 6 mo.	<ul style="list-style-type: none"> - protein energy malnutrition: subjective global assessment, BMI, albumin, arm muscle area - fat mass, fat-free mass (skinfold calipers/equations) - ICAM-1 - VCAM-1 - cytokines: CRP, TNFα, IL-6, irisin, - BMI, body fat percentage, FFM, - physical functioning: isokinetic knee extension/flexion, STS-10x, STS-60s 	<ul style="list-style-type: none"> ↓ in proportion of patients with protein-energy malnutrition ↑ nutritional status, BMI, fat-free mass, albumin, ↓ CRP, ICAM-1, VCAM-1, ↓ STS-10x ↑ STS-60s no Δ in any other outcome 	5
Bennett <i>et al.</i> , 2012 Australia	Inclusion criteria: ESRD, Age >18 yr; HD >3mo. Exclusion criteria: partial/total blindness, leg amputation, unable to understand English, hospitalized in previous month, unable to ambulate independently	PRT (n=24)	<p>Intradialytic PRT: hip abduction, ankle plantar/dorsi flexion, straight-leg raise, hip flexion, knee extension and flexion using elastic band and tubing.</p> <p>1 set x 10-20 reps at RPE 15-17. Loads increased when 20 reps performed, plus 10 minutes of static and dynamic balance exercises</p>	<ul style="list-style-type: none"> - falls risk computed from: reaction time, lower limb force, contrast sensitivity, proprioception, postural sway 	<ul style="list-style-type: none"> ↓ in falls risk score ↓ reaction time ↑ lower limb force no Δ in any other outcome 	5

pre- or post-dialysis (static and dynamic exercises of increasing difficulty), 2 x/wk, 8 wk

<p>Bullani <i>et al.</i>, 2011 Switzerland</p>	<p>Inclusion criteria: Age >18 yr; HD >3mo., adequate dialysis</p>	<p>PRT (n=11)</p>	<p>Intradialytic: flexion/extension at foot, knee and hip; hip abduction/adduction using elastic bands with 7 grades of resistance; initial 2-4 wk learning phase, then 3 sets x 20 repetitions at moderate RPE, resistance increased as tolerated, 2x/wk, 4.5-6 mo.</p>	<p>- physical functioning measures: Tinetti gait and balance instrument, 'timed up-and-go', one-leg balance, 6-min walk</p>	<p>↑ Tinetti score (gait and balance); ↓ 'timed up and go' - trend toward improved one leg balance (p=0.084) - trend toward improved 6-min walk (p=0.064) no Δ in any other outcome</p>	<p>5</p>
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Nindl et al. 2004, Headley et al. 2004 USA	Inclusion criteria: HD patients, physician approval. Exclusion criteria: renal osteodystrophy, recent MI or cardiovascular disease symptoms, uncontrolled cardiac dysrhythmias, hemodynamic instability, hypertension	PRT (n=10)	Non-dialysis time: leg press, knee extension/flexion, chest press, compound row, lateral raises, biceps curls, triceps extensions and abdominal curls. 1 set of 10-15 reps, 2x/wk, 12 wk	- anthropometric measures: body mass, body fat percentage, waist circumference - physical functioning: isokinetic knee extension strength at 90, 120 and 150 degrees/s, handgrip strength, 6-min walk, maximal gait speed, STS10x); - CRP -IGF-1; IGFBP-2, IGFBP-3 - growth hormone binding protein	↑ body fat percentage ↑ isokinetic strength at 90 degrees/s ↑ 6-min walk ↑ maximal gait speed ↓ STS10x, ↓ in CRP ↓ total and ternary IGF-1 no Δ in any other outcome	7
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Abbreviations: ESRD end stage renal disease, HD hemodialysis, Kt/V=hemodialysis treatment adequacy, PD peritoneal dialysis; PRT progressive resistance training, MI myocardial infarction, CVA cerebrovascular accident, HIV human immunodeficiency virus, AIDS acquired immune deficiency syndrome, RM repetition maximum, RPE rating of perceived exertion, MRI magnetic resonance imaging, STS sit-to-stand, HRQoL health-related quality of life, HDL-C high density lipoprotein cholesterol, LDL-C low density lipoprotein cholesterol, DEXA dual energy X-ray absorptiometry, CRP c-reactive protein, ADL activities of daily living, BMI body mass index, TC total cholesterol, CT=computed tomography, METS metabolic equivalent, TNF = tumor necrosis factor, IL interleukin, ICAM-1 intra-cellular adhesion molecule 1 (ICAM-1) VCAM-1 vascular cell adhesion molecule-1, IGF insulin-like growth factor

Table 4.2. Quality item assessment

Study Identification	Treatment Allocation (each worth 0.5 points): (1) evidence of randomization method; (2) evidence of concealment of treatment allocation	Were groups similar at baseline regarding the most important prognostic indicators?	Were the eligibility criteria specified?	Were outcomes assessors blinded?	Was compliance to the intervention reported?	Were exercise sessions supervised (0.5 for partial supervision)	Were dropouts reported?	Were point estimates and measures of variability presented for the primary outcome measures?	Did the analysis include an intention to treat analysis?	Were adverse events reported?	Total quality score (out of 10)
<i>Randomized controlled trials</i>											
Kirkman et al.	1	1	1	1	1	0	1	1	0	1	8
de Lima et al.	1	1	1	0	0	0.5	1	1	0	0	5.5
Song et al.	0.5	1	1	0.5	1	1	1	1	0	1	8
Orcy et al.	1	1	1	1	1	1	1	1	1	1	10
Dong et al.	0.5		1	0	1	1	1	1	0	0	6.5

Chen et al.	1	1	1	0	1	1	1	1	0	1	8
Afshar et al.	0	1	1	0	0	1	0	1	0	0	4
Segura-Orti et al.	0.5		1	1	1	1	1	1	0	0	7.5
Cheema et al.	1		1	0.5	1	1	1	1	1	1	9.5
Kopple et al.	0.5		1	0	0	1	1	1	0	0	5.5
Johansen et al.	1		1	0	1	1	1	1	0	1	8
<i>Within subjects + randomized controlled trial</i>											
Molsted et al.	1		1	0.5	1	1	1	1	1	1	9.5
<i>Uncontrolled trials</i>											
Moraes et al.	N/A	/A	1	N/A	0	1	1	1	0	1	5
Bennett et al.	N/A	/A	1	N/A	1	1	1	1	0	0	5
Bullani et al.	N/A	/A	1	N/A	0	1	1	1	0	1	5
Nindl, Headley et al.	N/A	N/A	1	N/A	1	1	1	1	0	1	6

Quality assessment

The quality assessment for the trials reviewed is presented in Table 4.2. RCT quality ranged from low (4/10) to high (10/10) with a mean quality score of 7.3/10, while 7/11 (64%) RCT had a quality score ≥ 7.5 . The trial by Molsted and colleagues had a quality score of 9.5/10. The four uncontrolled trials had a quality rating ranging from 5/10 to 6/10.

PRT interventions

Twelve trials prescribed lower body PRT exercises only (25, 26, 29-31, 35-40, 42-47) while four trials prescribed both upper- and lower body PRT exercises (19, 27). All studies prescribed two to three sessions of PRT per week, and 1 to 5 sets per exercise. Duration of training ranged from 8 weeks to 6 months. Four trials prescribed PRT outside of dialysis time (27, 28, 33, 34, 41, 48), while 12 trials prescribed PRT during dialysis (25, 26, 28-31, 33, 34, 36-40, 47, 48).

Outcomes

The 16 trials retrieved evaluated chronic adaptation to PRT across a range of clinically important outcomes, including: (1) skeletal muscle and protein-energy malnutrition, (2) physical functioning (i.e. muscular strength and power, and physical performance tests) (3) psychological health status, and (4) CVD risk factors (i.e. systemic inflammation, obesity, blood lipids and insulin resistance).

1. Skeletal muscle and protein-energy malnutrition

Nine trials (25, 27, 29, 30, 33-38, 42-46), including 7 RCT with a mean quality score of 7.6/10 (25, 27, 29, 30, 33-36), have investigated the effect of PRT on measures of skeletal muscle hypertrophy. Most recently, an RCT by Kirkman et al (25) prescribed three sessions of intradialytic PRT per week for 12 weeks performing a single resistance exercise (i.e. leg press) on a custom-designed machine providing a resistance of up to 200 kg. Participants performed three sets of 8-10 repetitions at 80% of predicted 1-repetition maximum (1RM) load. Load was increased with strength adaptation. The PRT group experienced a statistically significant increase in thigh muscle volume versus the control group [Mean Difference = 193 (95% CI = 63 to 324 cm³)].

Additional studies have shown that PRT prescribed for a minimum of 12 weeks, both during (30, 36-38) or outside of dialysis treatment (27, 45) can induce statistically significant increases in one or multiple measures of skeletal muscle hypertrophy. The hypertrophy noted in one uncontrolled trial (37) was concomitant with an improvement in nutritional status, evaluated *via* an increase in serum albumin ($p<0.05$) and the subjective global assessment score ($p<0.001$), and a decrease in the proportion of patients suffering from protein-energy wasting ($p=0.01$).

An RCT by Cheema et al (33, 34) (quality score = 9.5) prescribed intradialytic resistance training three sessions per week and documented a significant improvement in thigh muscle attenuation (a measure of muscle quality; $p=0.04$) and a clinically meaningful increase in thigh muscle cross-sectional area [Mean Difference = 2.1 (95% CI -1.9 to 6.1 cm²)]. These changes were accompanied by a significant increase in mid-arm ($p=0.004$) and mid-thigh ($p=0.04$) circumferences. In addition, a trend toward increased muscle cross-sectional area ($p=0.04$; non-

significant due to Bonferroni correction for two primary outcomes) was noted with a longer versus shorter duration of PRT (24 versus 12 weeks) (34).

In contrast to these positive findings, Dong et al (29) (RCT, quality score = 6.5) showed no change in whole body or leg muscle mass (both evaluated via dual energy X-ray absorptiometry) or circulating albumin or pre-albumin in patients prescribed 6 months of PRT and nutritional supplementation versus nutritional supplementation only. It was not clear if the PRT regimen in this study provided progressive overload. Similarly, Kopple et al (35) (RCT, quality score = 5.5) found no significant change in whole body muscle mass or thigh muscle cross-sectional area by prescribing a low-intensity (70-80% 5RM) PRT regimen for 21 weeks, but changes in anabolic genes expression including IGF-IEa mRNA and IGF-I protein ($p<0.05$) were noted. A controlled trial by Molsted et al. (45) using a biopsy of the vastus lateralis muscle, showed selective hypertrophy of the Type 2x muscle fibers concomitant with a reduction in the proportion of Type 2x fibers, and no effect on the other fiber types (i.e. Type 1, 2, and 2a).

Three studies of PRT in ESRD (38, 41, 43) have investigated anabolic hormone responses, including changes in circulating irisin, testosterone, luteinizing hormone, follicle stimulating hormone, estradiol, IGF-1, IGF-binding protein, sex hormone binding globulin and growth hormone binding protein. These studies found no effect except for a reduction in total ($p=0.039$) and ternary IGF-1 ($p<0.05$) in one small ($n=10$) uncontrolled trial (41).

2. Physical functioning

a. Muscular strength and power

Numerous studies have evaluated the effect of PRT on upper- (19, 27, 34), lower- (19, 25, 27, 29, 30, 32, 34, 36-38, 42-46, 49) and total body (33, 34) muscular strength in patients with ESRD. Eight of these trials were RCT (25-30, 32, 33, 35-38, 42-46) with a mean quality score of 7.9/10.

Cheema et al (33, 34) (RCT, quality score = 9.5) noted significant improvements in total body muscular strength (a summary of elbow extension, knee extension and knee abduction, assessed bilaterally and summed, $p=0.002$) in participants prescribed 12 weeks of full body intradialytic PRT (33). The authors also documented a significant increase in each of the isolated strength measures in their PRT group over time (all $p<0.001$) (34).

Only two additional studies, including one RCT (27) and one uncontrolled trial (19) have evaluated changes in upper body strength (i.e. maximal handgrip strength (assessed bilaterally)). Both studies prescribed a full body PRT regimen, either prior to routine hemodialysis treatment (27) or during non-dialysis time (19), and did not elicit a significant change in this outcome measure.

The effect of PRT on lower body strength has been consistent, with 9 of 11 studies (including 5 RCT, mean quality score = 8.2) documenting a significant increase in one or multiple measures of lower body strength secondary to PRT prescribed during dialysis (25, 30, 34, 36, 39, 47), just prior to dialysis sessions (27), or during non-dialysis time (42). Molsted et al (42) noted that the significant increase in 1RM knee extension strength ($p<0.001$) was concomitant with an increase in neuromuscular recruitment (EMG amplitude) and knee extension

power (i.e. rate of force development). Two trials documented no change in lower body strength measures (29, 37). Both studies did not state explicitly if the training loads were progressed with adaptation. In general, studies that have evaluated lower body strength using a dynamic or isometric test have shown significant adaptation, while studies utilizing a isokinetic dynamometer have shown mixed effects (19) or null (36, 37) effect on these outcomes.

b) Physical performance tests

Six trials have evaluated the effect of PRT on six-minute walk in patients with ESRD and have produced mixed results (19, 25, 28, 33, 34, 40, 47). One uncontrolled trial documented a significant increase in six-minute walk ($p < 0.05$) (19), while another uncontrolled trial noted a trend toward improvement ($p = 0.064$) (40). Two RCT noted a significant improvement in their PRT group over time (34, 47), but no significant group x time effect (33, 34, 47). Two additional RCT found no change in six minute walk secondary to >10 weeks of intradialytic PRT (25, 28).

Sit-to-stand performance tests have been evaluated in seven trials, including four RCT (19, 25, 32, 36, 37, 45). One RCT (30) (quality score = 8) noted a group x time effect for sit-to-stand performance. This finding has been supported by one controlled trial (45) (quality score = 9.5) and two uncontrolled trials (19, 37). Other RCT have documented only a within-group effect for their experimental group (47) or no effect (25, 36).

Additional physical performance tests that have been investigated have included ‘get-up-and-go’ (or ‘timed up-and-go’) tests (25, 40), gait speed (30, 36), Tinetti gait and balance (40), shoulder and waist flexibility (27), balance (27, 30, 40), falls risk (49), stair climbing (36), and sit-ups (27). In an uncontrolled trial, Bullani et al (40) prescribed 4.5 to 6 months of lower body intradialytic PRT and documented significant improvements in the Tinetti gait and balance test and the ‘timed up and go test,’ and trends toward improved one leg balance ($p = 0.084$). However,

these adaptations have not been noted in RCT assessing ‘get up and go’ (25), gait speed (30, 36), or single leg balance (27). Further, no effects have been noted for stair climbing (36), shoulder flexibility, trunk flexibility (sit and reach test) or sit ups (27). An uncontrolled trial by Bennett et al. (49) has provided evidence suggesting that 8 weeks of intradialytic PRT combined with balance exercises may significantly reduce falls risk by improving reaction time and lower limb strength.

c) Exercise capacity

Two studies have evaluated the effect of PRT on submaximal (26) and maximal exercise capacity (47). An RCT by de Lima et al (26) (quality score = 5.5) noted a significant increase in the number of steps achieved during a submaximal stepping test in their PRT group after 8 weeks of lower body intradialytic PRT ($p=0.0001$); however, group x time effects were not reported in this study. Similarly, an RCT by Segura-Orti (47) documented a significant increase in the metabolic equivalent exercise capacity during a graded exercise test to exhaustion within their PRT group following 24 weeks of lower body intradialytic PRT, however the group x time effect was non-significant.

d) Physical activity

Three RCT (30, 33, 36) have investigated the effect of intradialytic PRT on self-reported physical activity in patients with ESRD. One of these trials also employed the use of an accelerometer (36). Two of these studies (mean quality score = 8.8) yielded no effect secondary to 12 weeks of PRT (33, 36), while one study (30) yielded a significant increase in self-reported physical activity, a change driven primarily by a reduction in physical activity in the control group.

3. Psychological health status

Seven RCT (25-27, 30, 32-34, 36) and one controlled trial (45) (mean quality score = 8.0) have investigated the effect of PRT on one or multiple domains of HRQoL and/or other psychological outcomes (i.e. self-reported disability, fatigue, anger) in patients with ESRD. One or more domains of HRQoL have significantly increased in response to PRT in all except two trials (25, 32). Domains of HRQoL that have improved have included: physical functioning, (27, 30, 33, 36, 45), mental health (27, 30, 45), bodily pain, role emotional (45), vitality (33), social support, satisfaction, and general health (26).

An RCT by Cheema et al. (33) (quality score = 9.5) prescribed 12 weeks of full-body intradialytic PRT and demonstrated a trend toward reduced depression ($p=0.11$) in patients receiving PRT group as compared to usual care. Two other RCT (mean quality score = 8) have documented a trend toward improved fatigue ($p=0.06$) (36) and significantly reduced self-reported disability ($p=0.02$) (30) secondary to 12-24 weeks of lower body intradialytic PRT versus control.

4. Cardiovascular disease risk factors

a) Systemic inflammation

Seven trials have investigated the effect of PRT on circulating CRP in patients with ESRD (29, 31, 33, 35, 37, 41, 46). The results have been mixed. Three trials (31, 33, 37), including two RCT (31, 33), have reported significantly reduced CRP after 12 to 24 weeks of PRT, while three trials prescribing 16 and 24 weeks of PRT reported no change (29, 35, 46).

One uncontrolled trial of 8-week duration reported a reduction in CRP but did not statistically analyze this change (41).

Two trials (mean quality score = 7.5) that reported no change in CRP also reported no change in circulating IL-6 (44) or TNF- α (35). IL-6 and TNF- α also failed to change in two trials that noted significantly reduced CRP (37) (33). Cheema et al. (48) also noted no change in other pro- and anti-inflammatory cytokines, including IL-1b, IL-8, IL-10, and IL-12 secondary to 12 weeks of PRT versus control. Moraes et al (37) found that reduction of CRP ($p < 0.001$) was concomitant with significant reductions in the vascular cell adhesion molecule 1 (VCAM-1) ($p < 0.05$) and intra-cellular adhesion molecule 1 (ICAM-1) ($p < 0.05$).

b) Obesity

The effect of PRT on obesity outcomes in patients with ESRD has been inconsistent. Several trials have shown that PRT significantly increases BMI (37) and body mass (29, 33, 45), which is likely to be the product of muscular hypertrophy (33), while other studies including two RCT have reported no effect on these outcomes (19, 35, 36). Further, body fat percentage has also been shown to increase (19, 36), decrease (27, 30) or remain unchanged secondary to PRT (29, 35, 37). Only three studies to date have investigated the effect of PRT on measures of abdominal obesity including waist circumference (19, 27, 33) and visceral fat area (27). All of these studies have shown no effect.

c) Blood lipids

Two studies have investigated the effect of PRT on blood lipids in patients with ESRD (27, 31). An RCT by Song et al (27) (quality score = 8/10) prescribed full body PRT three sessions per week prior to each hemodialysis treatment for 12 weeks and documented

significantly reduced total cholesterol ($p=0.017$) and triglyceride ($p=0.012$) in the PRT group versus the control group. However, no change was detected in other blood lipids (i.e. HDL and LDL cholesterol). By contrast, a relatively low quality RCT by Afshar et al (31) (quality score = 4/10) documented no change in total cholesterol, triglyceride, or HDL or LDL cholesterol in participants prescribed 8 weeks of low intensity (60% 3RM) intradialytic PRT versus usual care ($n=7$).

d. Insulin resistance

A controlled trial by Molsted et al (46) completed a sub-group analyses limited to participants with impaired fasting glucose or type 2 diabetes and showed that 16 weeks of PRT significantly reduced circulating insulin concentrations (i.e. fasting, 2 hour postprandial, and total area under the curve, all $p<0.05$). However, there was no change in blood glucose or other parameters of insulin sensitivity (i.e. HOMA-2 or Matsuda Index).

4.5 Discussion

Summary and Recommendations

This systematic review has overviewed the current literature on PRT intervention in patients with ESRD. The evidence suggests that PRT can induce muscle hypertrophy, and improve aspects of physical functioning and HRQoL in this patient population. There is also preliminary evidence to suggest that PRT may reduce protein-energy malnutrition and cardiovascular risk factors, including CRP, total cholesterol, triglyceride, and measures of insulin resistance in patients with or at-risk of comorbid type 2 diabetes. These adaptations are clinically relevant to the ESRD population. Notably, guidelines for prescribing PRT across the chronic

kidney disease continuum have been included within a recent exercise prescription position statement (50), and we have recently indicated a need to update clinical practice guidelines to inform clinicians on the benefits of PRT in this cohort (51).

The evidence base for PRT adapting some of the endpoints investigated to date remains inconsistent (e.g. physical performance tests, obesity), and many other pertinent clinical outcomes remain to be investigated. Of the 16 clinical trials reviewed, 11 involved an RCT design. Seven RCT were of high methodological quality ($>7.5/10$), while four yielded a quality score $<6.5/10$. Particular methodological deficits across the lower quality RCT included the lack of blinded outcomes assessors, reporting of compliance to PRT intervention, conducting of intention-to-treat statistical analyses, and reporting of adverse events. Standardized reporting is required of future clinical trials (24, 52). It is also essential that PRT interventions be thoroughly described with respect to frequency, intensity, delivery (equipment and setting), supervision and application of progressive overload. This is particularly important for determining the exercise dose required to adapt specific endpoints (i.e. determine dose-response effects). Future trials also need to be limited to certain sub-populations with the ESRD population (e.g. patients with clinical depression, type 2 diabetes, hypercholesterolemia) to better elucidate the benefits of PRT on outcomes related to these specific comorbidities.

The majority of studies reviewed demonstrated significant skeletal muscle hypertrophy secondary to PRT. These findings are clinically important given that muscle wasting is common and a strong independent predictor of mortality in this cohort (53). Our findings are also supported by a recent meta-analysis showing that PRT can induce a regional hypertrophy (in targeted muscle groups) in patients with chronic kidney disease, including those receiving hemodialysis (SMD = 0.43 [95% CI = 0.11 to 0.76]) (11). Studies that have failed to elicit change in muscle hypertrophy measures have involved lower intensity training (35) or may have

failed to apply ongoing progressive overload (29). Evidence suggests that PRT with loads eliciting 6-12RM (with sets performed to the onset of neuromuscular fatigue and loading increased with strength gains) maximizes the hypertrophic response (54). Unfortunately, the equipment used in many trials prescribing intradialytic PRT specifically has been rudimentary (i.e. elastic tubing/bands, weighted ankle cuffs with a few kg loading) and may not optimize application of progressive overload. Only one trial reviewed developed a customized leg press machine for the dialysis setting with loading up to a maximum of 200kg (25). The patients enrolled in this study experienced similar myogenic adaptation to a group of healthy controls engaged in the same training regimen. Cheema et al. (55) have previously commented on the need to develop customized equipment, particularly targeting the lower body musculature, to deliver robust PRT regimens in the hemodialysis setting. A novel lower-body PRT device has been recently developed for in-center use by an Australian group and trialed in a study involving combined aerobic plus PRT (56). Regimens that maximize muscle hypertrophy through the optimal application of progressive overload are likely to target all muscle fiber types, in contrast to the findings of Molsted et al (45) which demonstrated only selective muscle fiber hypertrophy. Continuous progressive overload will also likely maximize the adaptation of other related outcomes, including muscle quality, metabolism, protein-energy malnutrition, and anabolic hormone and gene expression.

PRT-induced muscle hypertrophy may mediate the reduction of cardiovascular disease risk factors. For example, an RCT enrolling older patients with type 2 diabetes has shown that gains in muscle mass are significantly associated with reductions in CRP (57). This finding is also supported by the present review. Trials prescribing higher intensity PRT and demonstrating muscle hypertrophy (and reductions in protein-energy malnutrition) noted reductions in circulating CRP (33, 37) whereas trials prescribing less intense (35) or potentially non-progressive training (29) failed to induce muscle hypertrophy and hence reduce CRP. Greater

relative (to body size) muscle mass and quality are also associated with better insulin sensitivity and lower risk of type 2 diabetes (58, 59). Only one trial we reviewed has investigated the effect of PRT on insulin sensitivity outcomes (46) and showed some favorable results. RCT enrolling patients with ESRD and comorbid insulin resistance or type 2 diabetes are required to support these findings.

PRT-induced muscle hypertrophy and concomitant increases in energy turnover can also likely contribute to reduced body fat outcomes (e.g. body fat percentage and waist circumference) (60). To date, only two of seven studies have shown that body fat percentage can be significantly reduced secondary to PRT in patients with ESRD (27, 30), whereas none of three trials demonstrated a reduction in waist circumference (19, 27, 33) and visceral fat area (27). These outcomes require further investigation in a subset of ESRD patients with elevated body fat percentages and/or waist circumference.

Large-scale epidemiological studies have consistently identified low HDL, and high LDL and triglyceride as CVD risk factors in the general population (61-63). Dyslipidemia is also a significant risk factor for the progression of atherosclerosis and increased mortality (64, 65) in ESRD. Song et al (27) have shown that significantly reduced total cholesterol ($p=0.017$) and triglyceride ($p=0.012$) after PRT were accompanied by a positive shift in body composition (i.e. increased muscle mass and reduced body fat percentage). Hence, any null effect of exercise on lipids in several studies may be due to a lack of change in body composition as reported by Leehey et al (66). Additional research is required to ascertain the concurrent effect of PRT on lipid profile, body composition, arterial health and their interactions. Future studies should also investigate the effect of PRT on the usage of lipid-lowering medications as such medication use has been shown to be reduced in response aerobic training (67).

The effect of PRT on measures of lower body muscular strength have been consistent with most studies showing a positive effect (25, 27, 30, 34, 36, 39, 42, 47), however only three studies have evaluated changes in upper body strength and their effects have been inconsistent (19, 27, 34). The lack of improvement in upper body strength measured via maximal handgrip strength (19, 27) may have been due to the lack of exercises specifically targeting the forearm flexors. Another potential explanation is that the handgrip test is insensitive to changes with PRT. Only one study has documented an improvement in an upper body strength, measured via changes in maximal isometric forearm (i.e. triceps) extension (34). Future studies would benefit from the inclusion of more comprehensive and robust assessment of upper body muscular strength involving the major muscle groups of the upper body (e.g. chest and back muscles).

Several studies have shown an improvement in sit-to-stand performance secondary to PRT (19, 30, 37, 45, 47). In general, these studies prescribed PRT exercises at a relatively higher intensity, and include exercises that strengthen the major muscle groups associated with sit-to-stand performance (knee extensor, hip extensor and plantar flexor).

No controlled trials have noted improvements in the following physical performance tests: 'get up and go', gait speed, single leg balance, stair climbing, shoulder flexibility, trunk flexibility (sit and reach test) or sit ups. Many of these tests are highly dependent on motor agility, dynamic or static balance abilities (40, 68, 69). Although PRT is effective for improving lower body muscular strength (11), there may be a need to supplement PRT with other, more task-specific interventions (i.e. static balance, dynamic balance, standing and walking exercises) to improve these measures. This notion is supported by one uncontrolled trial (39) which combined lower body PRT with balance exercises and showed a reduction in falls risk.

Similarly, the effect of PRT on six-minute walk is inconsistent (19, 25, 28, 33, 34, 40, 47) and is likely to be a null effect unless the intervention includes more task-specific exercises. Only a significant increase of 25m was found in one uncontrolled trial (19). This is less than the smallest improvement (~43m to 54m) necessary for a clinically meaningful change in patients with chronic obstructive pulmonary disease and heart failure (70). Since six-minute walk is a proxy-measure of aerobic exercise capacity (68), the lack of improvement in this outcome could be due to the limited stress of PRT on aerobic fitness. To date, there is no RCT evidence to suggest that isolated PRT can improve aerobic fitness. Similarly, evidence for PRT increasing or changing physical activity levels is also lacking.

One or multiple domains of HRQoL have been shown to improve in five of seven RCT (26, 27, 30, 33, 34, 36). The lack of improvement of HRQoL domains in two trials (25, 47) may be due to their patients being similar in HRQoL measures versus their age-matched healthy peers (25). Impaired HRQoL and increased mortality has also been linked with depression in hemodialysis patients (71). Patients with ESRD are also prone to depression which are commonly undertreated (72). To date, there is very little evidence that PRT can treat depression or other psychological impairments. Therefore, more research trials on PRT in patients with ESRD suffering from depressive symptoms and other mental health conditions are needed. These studies need to elucidate on the dose-response effects of PRT across a range of psychological outcomes in these ESRD subgroups.

In conclusion, this systematic review has provided an overview of the extant literature on PRT in patients with ESRD, and outlined many recommendations future RCT. Trials are required to investigate a range of novel research questions related to the benefits and application of PRT in this cohort and its subgroups (e.g. patients with diabetes, depression, dyslipidemia, etc.). Future studies are required to be of high methodological quality to inform clinical practice

guidelines to effectively enhance the important patient outcomes, including morbidity, mortality and HRQoL.

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Chapter 5

Development, Feasibility and Efficacy of A Customized Exercise Device To Deliver Intradialytic Resistance Training In Patients with End Stage Renal Disease

5.1 Abstract

Introduction: This study assessed the feasibility and efficacy of a novel training device used within an intradialytic progressive resistance training (PRT) intervention.

Methods: Non-randomized, within-subjects crossover design with outcomes assessed at baseline (week 0), post-control (week 13) and post-PRT intervention (week 26). Twenty-two hemodialysis patients (59% men, 71 ± 11 years) performed PRT three sessions per week for 12 weeks. The resistance training device was developed to enable the performance of 2 upper and 3 lower body exercises, unilaterally and bilaterally, both before and during dialysis with loads of 2.5 to 59 kg. Feasibility outcomes included adverse events, adherence and training load progression. Changes in upper and lower body muscular strength, six-minute walk, health-related quality of life (HRQoL) via the Short-Form 36 and Geriatric Depression Scale were evaluated.

Findings: The PRT intervention was delivered without serious adverse events, resulted in $71.2 \pm 23.3\%$ adherence and significant adaptation of all training loads from pre to mid to post training (83.8% to 185.6%, all $p < 0.05$). Lower body strength ($p < 0.001$) and HRQoL sub-scales (Role-Physical, Social Functioning, Role-Emotional) significantly increased (all $p < 0.01$) and a trend toward reduced depression was noted ($p = 0.06$). No significant changes were noted in other outcomes.

Discussion: PRT using the novel training device was feasible and improved measures of physical and psychological health and HRQoL. This device can be utilized in most dialysis centers. Future studies are required to evaluate dose-response effects of PRT prescriptions in subpopulations, and PRT in standard dialysis practice.

5.2 Introduction

The global incidence of end-stage renal disease (ESRD) continues to rise annually (1). This trend is being driven by an unprecedented burden of hypokinetic diseases, particularly the type 2 diabetes-obesity pandemic (2). As the ESRD patient population continues to grow, greater efforts must be directed toward improving important patient outcomes in this cohort, including physical functioning and health-related quality of life (HRQoL).

Progressive resistance training (PRT) is an exercise modality that can counteract many physiological, functional and psychological impairments caused by ageing and disease (3). Studies have shown that PRT can treat metabolic diseases, including type 2 diabetes mellitus (T2DM) and obesity (4-6). Early studies in patients with ESRD prescribed PRT interventions during non-dialysis time and resulted in low participant enrollment and adherence (7). More recently, PRT interventions have been prescribed during dialysis (8-10) in an attempt to overcome some of the barriers to exercise participation, including lack of access and time (7). This evidence suggests that intradialytic PRT can improve many important aspects of health status (11). However, its delivery must be refined to elicit better health adaptations and enable seamless translation into standard clinical care (12).

To date, exercise equipment used for intradialytic PRT within clinical trials had been largely rudimentary (12). Lower body exercises have typically been prescribed using weighted ankle cuffs (8, 10, 13), and upper body exercises have either been avoided due to perceived difficulty (9), or prescribed unilaterally during dialysis in the non-fistula containing arm using elastic bands (14) or dumbbells (15), with the fistula-containing arm trained with the same exercises just prior to each dialysis session. Utilizing these rudimentary forms of equipment is cost-effective, but can compromise PRT effectiveness (12). For example, ankle cuffs typically have a low loading capacity (up to 10 kg), and patients who have achieved the maximum load for

a PRT exercises will experience no further overload and hence limit adaptation (12). Moreover, the use of dumbbells during dialysis restricts a patient to performing only a few exercises that do not effectively target the major muscle groups of the upper body, e.g. pectorals or latissimus dorsi (12). Experts have previously suggested a need to develop and evaluate the effects of more robust training devices to enhance the delivery of intradialytic PRT (16).

The purpose of this study was to present the invention of a prototype, customized resistance training device and assess its feasibility and efficacy in a comprehensive intradialytic PRT intervention in conventional hemodialysis units. Feasibility outcomes in this study included the assessment of adverse events, adherence, and training intensity (loads). Efficacy outcomes included measures of physical functioning (i.e. muscular strength and exercise capacity) and psychological health status (i.e., HRQoL and depression).

5.3 Methods

Study Design

This study utilized a within-subjects, non-randomized crossover design comparing the outcomes of an initial 12-week usual care control period to a 12-week intradialytic PRT intervention period. Outcome measures were assessed at baseline (week 0), after the control period (week 13) and after the intervention period (week 26). The Western Sydney University Human Research Ethics Committee (Research Code: H9651) and the Central Northern Adelaide Health Service (RAH Protocol No.: 120507) approved all research procedures, and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000496819).

Participants

Eligibility criteria: (1) adult aged ≥ 40 years, (2) medically stable and adequately dialyzed ($Kt/V \geq 1.2$) for greater than three months, (3) able to ambulate independently or with an assistive device for ≥ 50 m, (4) no amputation, (5) no acute or chronic medical condition that contraindicated or prevented the performance of PRT during hemodialysis treatment, (6) cognition and English language sufficient to understand research procedures and provide written informed consent, (7) sedentary (i.e., less than 120 min of moderate-intensity physical activity per week), (8) no recent participation in PRT. Participants were recruited from four outpatient hemodialysis centers in South Australia from 2012 to 2013. All patients were evaluated for eligibility, which involved review of the medical records, clearance from the nephrologist, and interview of the patient.

Prototype design and development

The lead author (D.C.) developed the prototype in consultation with Maxim Strength Fitness Equipment Pty. (www.maximfitness.net), Adelaide, Australia (Figure 5.1). The lead author is an accredited exercise physiologist (18) who has worked for over six years prescribing exercise as standard care in dialysis centers in the Adelaide metropolitan area. In clinical practice, the lead author routinely utilized a custom-designed resistance training device developed and tested by Bennett et al. (19). The device consisted of a weight-adjustable, pulley system that applied resistance (up to 32 kg) to the lower body musculature in three movements: leg press, knee flexion and knee extension (19). The prototype designed in the present study advanced upon this initial design (19) by enabling the performance of both upper and lower body exercises during dialysis with heavier loads.

The lead author first conceptualized and sketched an equipment design that was portable and could provide an overload stimulus to all major muscle groups. To ensure portability, the space available in participating dialysis centers and the dimensions of standard hemodialysis chairs (Fresenius Medical Care, Scoresby, Victoria, Australia) were considered. The concept from Bennett et al. (19) of a portable device with wheels and brakes was adopted to allow safe positioning during pre-dialysis and intradialytic training, or stowed aside when not in use. The exercises needed to be administered without complicated set-ups or configuration changes, easily used in practice by either exercise physiologists or dialysis nursing staff.

The structure was made of steel and measured 1.16 m wide, 0.94 m long and 1.61 m tall. The design consisted of a trapezium-shaped base, with two lever arms pivoting from the corners of the widest side and the pin-loaded weight stack is positioned on the shorter side (Figure 5.1a and 5.1b). The lever arms allowed the performance of resistance exercises unilaterally or bilaterally, involving pushing (chest press) and pulling (seated row, hip flexion) while a plate

attachment was connected to a pair of steel cables enabling leg press and knee flexion exercises. All exercises performed with the device are presented in Figure 5.2. Loading of each exercise ranged from 2.5 to 59 kg; the weights were pin-loaded and easily adjusted. One kg add-on weights were available for gradual increment increases (Figure 5.1c).

Figure 5.1. Custom-designed training device

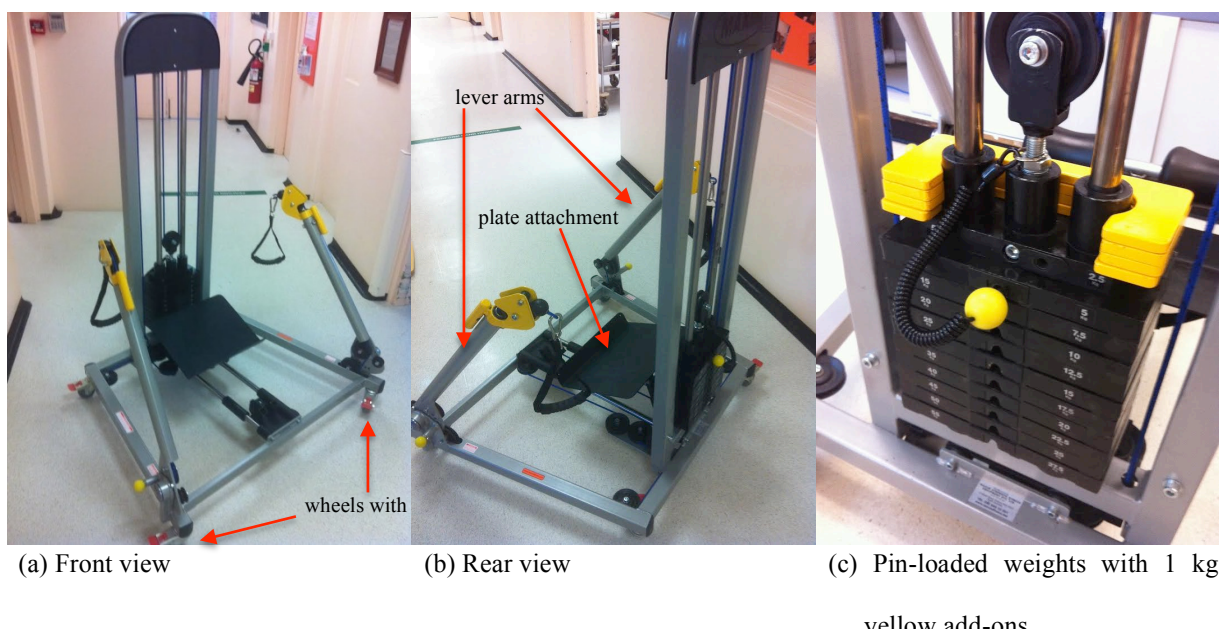


Figure 5.2. Resistance training exercises performed with the customized exercise device.

(a) seated row with machine, (b) chest press with machine, (c) leg press with machine, (d) knee flexion with machine, (e) hip flexion with machine



(a)



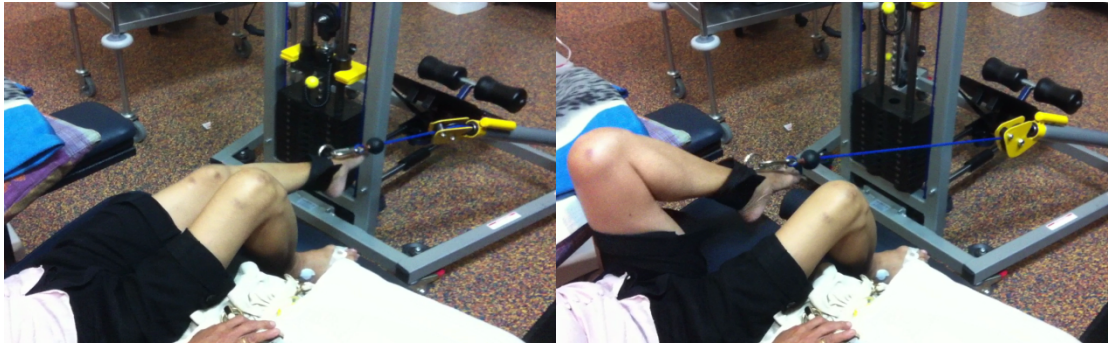
(b)



(c)



(d)



(e)

Intervention

Participants were prescribed a full-body PRT program three times per week (36 sessions in total) supervised by an exercise physiologist (20). The upper limb containing the vascular access was exercised prior to each dialysis session with the patient seated in the waiting area, while all other exercises were performed with the patient in a seated or supine position in a standard hemodialysis chair (Fresenius Medical Care, Scoresby, Victoria, Australia). The intradialytic exercises were completed during the first half of each hemodialysis session. Smaller muscle groups that were not isolated by the exercise device, including the biceps, triceps, and deltoids were targeted by free weight dumbbells (Celsius™, China) or Thera-band™ elastic tubing (Akron, Ohio, USA). During the first four weeks of PRT, three sets of 12-15 repetitions of each exercise were performed at a rating of perceived exertion (RPE) of 12-14. During the latter eight weeks of PRT, three to four sets of 10-12 repetitions of each exercise were performed at a RPE of 14-15 (21). The duration of the training session was approximately 30 minutes by alternating, set-to-set, exercises that targeted different muscle groups.

Feasibility outcomes

Adverse events

Adverse events related to exercise participation and all visits to health care professionals occurring during the control and intervention periods were documented weekly using a structured questionnaire and reviewing the clinical notes. An adverse event was defined as any injury, impairment or medical condition that was directly or suspected to be due to performing the prescribed exercise.

Adherence

Overall adherence to training was computed as the total number of exercise sessions attempted divided by the total number of exercise sessions offered, multiplied by 100%. In

addition, the percentage of each of the 10 prescribed PRT exercises completed was computed as the total number of sets completed divided by the total number of sets prescribed, multiplied by 100%. Reasons for missing or non-attempt of exercise sessions were also documented.

Training load (intensity)

The heaviest training load lifted during the first-, mid- (session 18) and final session (session 36) of the 12-week PRT intervention period was collected and noted for each exercise performed using the resistance exercise device and dumbbells.

Physical functioning

Upper body muscular strength was evaluated using a hydraulic handgrip dynamometer (Seahan SH5001, Heanor, UK) and standard procedures (22). High intra-examiner reliability (right: $r=0.981$, left: $r=0.985$) for the dynamometer has been reported for both arms (23). A composite measure of lower body muscular strength was evaluated using a three-repetition maximum test using the resistance exercise device and standard test protocols (24). The test was performed unilaterally with the right and left leg added to create a summary score. The six-minute walk test was used as an index of exercise capacity (25).

Psychological health status

The Short Form 36 (SF-36) Version 1.0 questionnaire was used to evaluate changes in eight sub-scales of HRQoL, including *Physical Functioning*, *Role Physical*, *Bodily Pain*, *General Health*, *Vitality*, *Social Functioning*, *Role Emotional and Mental Health* (26). The instrument also provides domain scores for *Physical Component Summary* (PCS) and *Mental Component Summary* (MCS) calculated from the relevant HRQoL sub-scales.

The Geriatric Depression Scale (GDS) was used to evaluate depression symptoms with scores categorized as: 'normal' (0 – 9), 'mild depression' (10-19), and severe depression (20-30)

(27). The GDS is accepted as a reliable and valid self-rating depression screening scale for elderly populations (28) and in adults younger than age 65 (29).

Statistical Analysis

Analyses were performed using SPSS (IBM©, Version 19.0). All data were inspected visually and statistically for normality at each time point (weeks 0, 13, and 26). Normally distributed data were described using mean \pm standard deviation. Non-normally distributed data were log-transformed (\log^{10}) across the three time points prior to entry into parametric statistical models. Primary analysis incorporated a linear mixed model defining individual as the random effect with the outcome measure evaluated across three time points (weeks 0, 13, 26). All data were included regardless of participant adherence to the intervention according to the intention-to-treat principle (n=22). Each model was also adjusted for age, gender, dialysis vintage, and interactions for time by age, time by gender and time by dialysis vintage. P-values were reported for the change from week 0 to week 13 and change from week 13 to 26. In addition, the mean difference and effect size were computed comparing the control period (week 13 – week 0) to the intervention period (week 26 – week 13). Changes in training intensity (loads) over time were evaluated by paired t-tests for all exercises performed using the customized exercise device and dumbbells. A p-value of <0.05 and a 95% CI exclusive of zero were accepted as statistically significant.

5.4 Results

Participants and recruitment

Twenty-two eligible participants consented to participate and completed baseline assessment, comprising 11% of the patient population reviewed across the four outpatient hemodialysis centers (n=195; Figure 5.3). Baseline characteristics of the cohort are presented in Table 1 and participant flow chart in Figure 5.3.

Feasibility outcomes

Adverse Events

One participant experienced dizziness once while exercising during hemodialysis. Although blood pressure was normal, exercise was immediately ceased. There were no other adverse events.

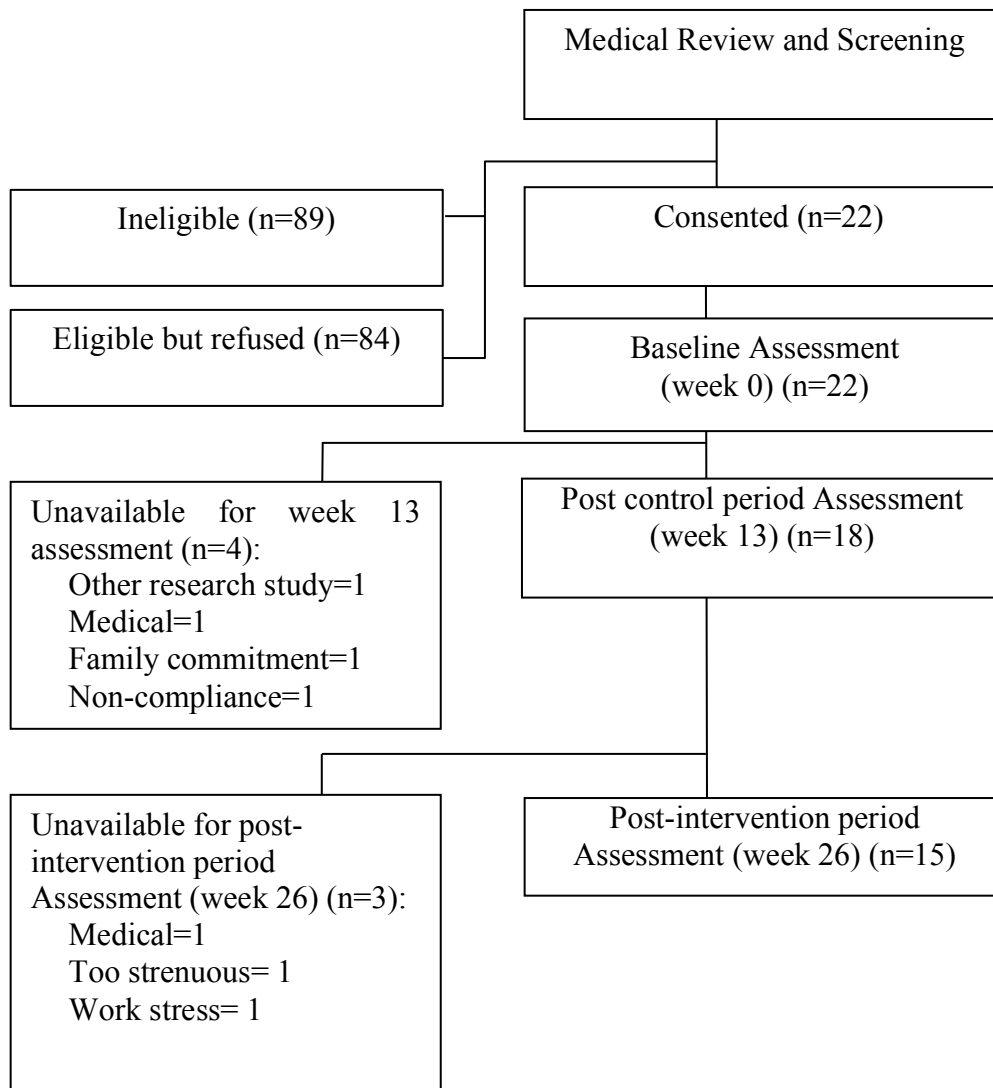
Adherence

Adherence to PRT in the 18 participants who undertook the intervention was $71.2 \pm 23.3\%$. Eleven of 18 participants achieved at least 75% adherence (i.e., greater than 27 of 36 sessions attended). Three participants who refused follow-up assessment at week 26 completed less than 20% of the PRT intervention. The main reasons cited by participants for not attempting an exercise session included hospitalization or acute illness. The percentage completion of exercises using the resistance exercise device ranged from 61.6% to 68.6%, while the percentage of exercises completed using the dumbbells and elastic bands ranged from 51.4% to 67.7% (Table 5.2).

Training load (intensity)

All training loads for all exercises performed using the customized device and dumbbells significantly increased from session 1 to session 18, and session 18 to session 36, and from pre to post training (session 1 to session 36; all $p < 0.05$; Table 2). The change in training intensity from session 1 to session 36 across all exercises ranged from $83.8 \pm 56.5\%$ to $185.6 \pm 121.0\%$. The percentage adaptation in loading was similar between exercises using the customized device and the dumbbells.

Figure 5.3. Participants flow



Physical functioning

Leg press strength increased significantly from the control to PRT intervention period [Mean Difference = 10 (95% CI = -1 to 21); $p < 0.001$, effect size (ES)=0.55]; however, no change was noted in the maximal handgrip strength of the fistula or non-fistula containing arm (Table 5.3). Six-minute walk did not significantly change from the control to the intervention period (Table 5.3).

Psychological health status

Significant improvements with large relative effect sizes were noted from the control to the PRT intervention period in several sub-scales of HRQoL, including: *Role Physical* [Mean Difference = 14.6 (95% CI = 8.4 to 20.8); $p = 0.035$, ES=1.41], *Social Functioning* [Mean Difference = 24.5 (95% CI = 10.3 to 38.7); $p = 0.029$, ES=1.03] and *Role Emotional* [Mean Difference = 17.4 (95% CI = 12.3 to 22.5); $p < 0.001$, ES=2.04]. There were also significant decreases in *Role Physical* and *Role Emotional* health sub-scales from pre-control to post-control time points (Table 4). There was also a trend toward an increase in the MCS [Mean Difference = 6.7 (95% CI = 1.2 to 12.3); $p = 0.07$, ES= 0.72] and a decrease in GDS [Mean Difference = -4.3 (95% CI = -7.7 to -1); $p = 0.061$, ES= -0.77] from the control and intervention periods.

Table 5.1. Baseline characteristics of the total cohort (n=22)

Age (years)	71.3 ± 11.0
Sex (men: women)	13:9
Ethnicity	
Caucasian, <i>n</i> (%)	17 (77.3)
Asian, <i>n</i> (%)	1 (4.5)
Aboriginal, <i>n</i> (%)	2 (9.1)
Indian, <i>n</i> (%)	2 (9.1)
Height (cm)	161.4 ± 10.4
Body weight (kg)	74.6 ± 17.9
Body Mass Index (kg/m ²)	28.5 ± 5.6
Dialysis vintage, months (range)	42.5 (7 – 163)
Systolic blood pressure at rest (mm Hg)	149 ± 24
Diastolic blood pressure at rest (mm Hg)	68 ± 9
Dialysis adequacy (Kt/V)	1.72 ± 0.26
Serum creatinine (µmol/L)	706.2 ± 141.8
Serum albumin (g/L)	35.6 ± 2.3
<u>Medications, <i>n</i> (%):</u>	
Erythropoiesis stimulating agents	18 (81.8)
Beta blockers	11 (50.0)
Calcium channel blockers	11 (50.0)
Nitrates	4 (18.2)
Angiotensin-converting enzyme inhibitors	3 (13.6)
Alpha blockers	3 (13.6)
Angiotensin II receptor blockers	1 (4.5)
Tobacco use history (<i>n</i>)	11
Etiology of kidney failure	
other, <i>n</i> (%)	12 (54.5)
diabetes, <i>n</i> (%)	7 (31.8)
hypertension, <i>n</i> (%)	2 (9.1)
glomerular diseases, <i>n</i> (%)	1 (4.5)

Data reported as mean ± standard deviation except dialysis vintage (median value and range reported due to non-normal distribution). Dialysis adequacy (Kt/V) greater than or equal to 1.2 is considered adequate.

Table 5.2. Adherence to specific exercises and training intensity (load)

Equipment	Exercises	Sets Completed (%)	Session 1 load (kg)	Session 18 load (kg)	Session 36 load (kg)	%change (session 1 to 18)	%change (session 18 to 36)	%change (session 1 to 36)
Customized device	Chest press	67.7 ± 29.1	4.0 ± 2.3	5.8 ± 3.4 ^a	8.8 ± 4.5 ^{b,c}	53.3 ± 69.5	62.7 ± 72.4	140.0 ± 131.2
	Seated row	67.2 ± 28.8	8.6 ± 6.4	13.8 ± 8.1 ^a	18 ± 9.2 ^{b,c}	68.6 ± 47.0	38.6 ± 41.8	133.6 ± 90.9
	Leg press	68.6 ± 28.4	25.7 ± 5.5	40.9 ± 12.2 ^a	58.1 ± 19.8 ^{b,c}	57.3 ± 38.8	40.9 ± 23.3	123.1 ± 74.7
	Knee flexion	67.5 ± 28.0	10.5 ± 3.4	15.7 ± 2.6 ^a	19.9 ± 3.2 ^{b,c}	44.3 ± 40.7	28.4 ± 17.7	83.8 ± 56.5
	Hip flexion	61.6 ± 29.8	2.3 ± 1.5	5.4 ± 3.3 ^a	6.8 ± 3.5 ^{b,c}	119.4 ± 134.3	45.4 ± 32.0	185.6 ± 121.0
Dumbbells	Shoulder press	65.6 ± 29.6	2.7 ± 0.9	4.8 ± 1.0 ^a	6.5 ± 1.3 ^{b,c}	79.6 ± 55.2	37.7 ± 20.6	142.8 ± 66.2
	Biceps curl	67.7 ± 28.4	3.0 ± 1.0	5.2 ± 1.2 ^a	6.7 ± 1.1 ^{b,c}	76.3 ± 54.5	32.3 ± 17.9	130.2 ± 66.8
Elastic tubing	Triceps extension	60.6 ± 25.7						
	Back extension	51.4 ± 30.8	N/A	N/A	N/A	N/A	N/A	N/A
	Knee extension	63.5 ± 27.2	N/A	N/A	N/A	N/A	N/A	N/A

Data reported as mean ± standard deviations. N/A not applicable.

^asignificant increase from session 1 to 18

^bsignificant increase from session 18 to 36

^csignificant increase from session 1 to 36

Table 5.3. Physical functioning and psychological health status outcomes

Outcome Measure	Week 0	Week 13	Week 26	<i>P</i> (time)	<i>P</i> (week 13 vs 0)	<i>P</i> (week 26 vs 13)	Mean Difference (95%CI) (Intervention - Control period)	Relative ES (95% CI) (Intervention period - Control period)
<i>Physical functioning</i>								
Handgrip strength, fistula (kg)	19 ± 5	19 ± 5	19 ± 6	0.44	0.32	0.93	-1 (-4, 3)	-0.13 (-0.72, 0.47)
Handgrip strength, non-fistula (kg)	20 ± 6	20 ± 6	21 ± 6	0.92	0.91	0.31	1 (-3, 4)	0.12 (-0.47, 0.71)
Lower body strength (kg)	62 ± 18	64 ± 18	77 ± 21	0.69	0.31	<0.001	10 (-1, 21)	0.55 (-0.05, 1.16)
Six-minute walk (m)	328 ± 90	331 ± 96	317 ± 108	0.51	0.90	0.49	-16 (-72, 41)	-0.17 (-0.76, 0.43)
<i>Psychological health status</i>								
<i>1. Health-related quality of life</i>								
Physical Functioning	48.7 ± 25	43.2±25.9	46.5±29	0.11	0.24	0.54	8.7 (-6.8, 24.2)	0.33 (-0.26, 0.93)
Role-Physical	14.7 ± 9.9	6.4±10.5	12.7±12.2	0.53	0.002	0.04	14.6 (8.4, 20.8)	1.41 (0.75, 2.07)
Bodily Pain	55.8 ± 28	60.6±28.9	62.6±32	0.44	0.32	0.71	-2.7 (-20, 14.6)	-0.09 (-0.68, 0.5)
General Health	46.7 ± 16.7	52.4 ± 17.4	48.2±19.7	0.68	0.10	0.28	-9.8 (-20.1, 0.6)	-0.56 (-1.16, 0.04)
Vitality	50.4 ± 23.2	47.9 ± 24.5	54.9±28.1	0.34	0.63	0.25	9.6 (-4.9, 24.2)	0.4 (-0.2, 0.99)
Social Functioning	78.0 ± 22.7	68.3 ± 24.0	83.0±27.8	0.61	0.10	0.03	24.5 (10.3, 38.7)	1.03 (0.4, 1.66)
Role-Emotional	21.2 ± 8.1	13.6 ± 8.6	23.5±10.1	0.30	0.002	<0.001	17.4 (12.3, 22.5)	2.04 (1.31, 2.77)

Mental Health	83.7 ± 17.9	82.8 ± 19	89.8±22.1	0.27	0.86	0.20	7.8 (-3.4, 19.1)	0.42 (-0.18, 1.01)
Physical Component Scale	31.7±7.4	31.7±7.7	31.3±8.5	0.51	0.99	0.80	-0.4 (-4.9, 4.2)	-0.05 (-0.64, 0.54)
Mental Component Scale	49.8±8.9	47.9±9.4	52.8±10.9	0.41	0.41	0.07	6.7 (1.2, 12.3)	0.72 (0.11, 1.33)
<i>2. Depression</i>								
Geriatric Depression Scale	6.8±5.3	8.5±5.7	5.9±6.3	0.19	0.15	0.06	-4.3 (-7.7, -1)	-0.77 (-1.39, -0.16)

Data reported as mean ± standard deviations. The mean difference expresses the mean difference in the outcome between the control and intervention periods. The relative effect size is the mean difference between the two periods divided by the pooled standard deviation of the outcome at baseline among participants. A p-value of <0.05 and a 95% CI exclusive of zero were accepted as statistically significant.

5.5 Discussion

This study presents on the development, feasibility and efficacy of integrating a customized resistance training device within a conventional hemodialysis unit. The intervention was delivered without serious adverse events, resulted in a moderate-to-high level of adherence and positive adaptation in training loads. Exercising patients also significantly increased lower body muscular strength and several sub-scales of HRQoL, including *Role Physical*, *Social Functioning*, and *Role Emotional*. Trends toward improved *Mental Component Summary* and reduced depression evaluated via the Geriatric Depression Scale were noted.

To our knowledge, there have been only two studies that have implemented the use of novel resistance training device in the hemodialysis setting (9, 19). However, both devices could only target the lower body musculature with either one (9) or a few movements (19) and this has been identified as a major limitation of PRT interventions prescribed to date (12). Hence, this study developed a device to exercise both the upper and lower body musculature in the dialysis setting. Upper body exercises included the chest press and seated row that targeted the pectoral and back muscles. The improvement of training loads for all exercises delivered with our device (Table 1) indicated that progressive overload was being applied without a plateau in training intensity (loading). Targeting all muscle groups and providing ongoing application of progressive loading are arguably the most critical aspects of effective PRT delivery, and this finding therefore highlights the feasibility of using this novel device in the hemodialysis setting.

The current study is based on recommendations to implement intradialytic exercise to enhance exercise uptake and adherence in patients with ESRD (16). However, as intradialytic PRT was still uncommon and often unheard of by patients, exercise uptake remained low with about 1 out of 4 eligible patients agreeing to participate in the current study (Figure 5.3). Over 43% (84/195) of the patients reviewed were not interested in participating in this study. Low

enrollment in PRT intervention trials is not uncommon, with recruitment rates ranging between 17 to 34% of patients reviewed (9, 10, 13-15, 30-32).

This highlights the difficulty in implementing intradialytic PRT. To sustain such a program in clinical practice, it is likely that recommendations for exercise participation will have to come from consulting nephrologists and reinforced by other clinicians, including the dialysis nursing staff and exercise professionals (33). The literature supports incorporation of exercise into dialysis sessions as standard practice, based on 30 years of evidence (34, 35). However, barriers to such implementation exist including lack of awareness of benefits by health care professionals and patients, fears of injury, perceived burdens of integration with dialysis activities, and availability of accessible and affordable equipment and trainers. These aspects of translation need to be investigated further, as well as the nexus between exercise professionals and dialysis nursing staff to adequately deliver intradialytic PRT.

The current study has overcome the difficulty of performing upper body exercises in the hemodialysis setting by incorporating a customized exercise device and secondary modalities to perform the exercises unilaterally during dialysis or prior to hemodialysis. Adding upper body exercises did not hamper adherence or increase adverse events compared to earlier trials of lower body exercise (10, 13, 14). Consistent with our findings, a recent meta-analysis found no evidence of serious adverse events secondary to PRT prescribed across the chronic kidney disease continuum, including in patients with ESRD (33) and adherence to PRT across previous studies has ranged from 59%(8) to 94% (9).

The improvement of lower body muscular strength is consistent with the majority of studies prescribing PRT interventions during (8-10, 31, 32, 36) or outside (37, 38) routine hemodialysis treatment. Only two trials have documented no change in lower body strength

measures (39, 40) and both studies did not state explicitly if the training loads were progressed with adaptation. The improvement in lower body strength in this study is an important finding as poor lower body muscular strength is associated with reduced muscle mass (41) and increased risk of falls (42, 43). Intervention studies prescribing PRT across the chronic kidney disease continuum have been shown to increase muscle mass (33), and reduce the risk of falls (32).

The lack of improvement of handgrip strength is consistent with the literature, as two previous studies also reported no change in this outcome secondary to 12 weeks of isolated full body PRT (37, 44). The lack of adaptation could be attributed to the lack of exercises for forearm flexors. Another potential explanation is that the handgrip test is insensitive to changes with PRT as the increments in training load over time did suggest upper body strength gain in the current cohort. To date, only Cheema et al (8) have documented an improvement in an upper body strength following a 24-week intradialytic PRT intervention in hemodialysis patients, measured via changes in maximal isometric forearm (triceps) extension. Future studies would benefit from the inclusion of more comprehensive and robust assessment of upper body muscular strength involving major muscle groups.

Similarly, the lack of improvement in six-minute walk is also consistent with the mixed results in the literature. One uncontrolled trial has noted a significant increase in six-minute walk ($p < 0.05$) (44), while another uncontrolled trial noted a trend toward improvement ($p = 0.064$) (45). Two RCTs have noted a significant improvement in their PRT group over time (8, 36), but no significant group x time effects (8, 15, 31, 36). Two additional RCTs found no change in six minute walk secondary to >10 weeks of intradialytic PRT (9, 14). Additional studies are warranted to determine the relative importance of physiological constructs most limiting to six-minute walk performance in this cohort (e.g., poor balance, low aerobic capacity, muscle weakness, fear of falling, musculoskeletal pain, claudication, etc.), in order to design exercise

interventions to more specifically target the relevant deficits.

As low HRQoL and depression are associated with increased mortality in hemodialysis patients (46, 47), HRQoL was also assessed in this study. At baseline (week 0) and post-control (week 13), the mean score for all eight health sub-scales of SF-36 except mental health were lower than available data for South Australian general population age-matched norms (48). Mental health was similar to the age-matched norms at all time points. Among the eight health sub-scales measured using the SF-36 health survey, *Role Physical* ($p=0.035$; ES=1.41), *Social Functioning* ($p=0.029$; ES=1.03) and *Role Emotional* ($p<0.001$; ES=2.04) were significantly improved with a large effect size post-exercise (week 26) compared to post-control (week 13). Despite the improvements, these health sub-scales remained lower than the normative data for the South Australian population (48). Nevertheless, these improvements plus near-significant improvements post-treatment in depression and the *Mental Component Summary* suggest that PRT can benefit patient emotional well-being. This is consistent with most PRT studies in ESRD that have shown improvements in one or multiple sub-scales or domains of HRQoL (8, 10, 13, 31, 37). Future studies should specifically investigate patients who have clinically significant levels of depression to determine whether exercise benefits for this condition extend to the depressed dialysis cohort.

In summary, the findings of this study suggest that PRT using our customized exercise device is feasible and can improve aspects of physical functioning and psychological health status. The exercise device tested in this study can be utilized in most dialysis centers with sufficient space to give patients the option of PRT before or during dialysis. Future studies are required to determine dose-response effects of comprehensive PRT prescriptions in various subpopulations of ESRD (e.g., in those with type 2 diabetes or clinical depression), and evaluate

the staff and training requirements to allow translation of intradialytic PRT into standard clinical practice.

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Chapter 6

Effect Of Intradialytic Progressive Resistance Training On Arterial Stiffness And Associated Biomarkers In Patients With End Stage Renal Disease: A Non-Randomized Controlled Crossover Trial

6.1 Abstract

Background: This study investigated the effect of a 12-week intradialytic progressive resistance training (PRT) intervention on arterial stiffness (pulse wave velocity, PWV), hemodynamic and associated biomarkers in patients with end stage renal disease (ESRD).

Study design: Non-randomized, within-subjects crossover design comparing change over an initial 12-week control period with a 12-week intervention period. All outcomes were assessed at baseline (week 0), post-control (week 13) and post-intervention (week 26).

Setting & Participants: 22 patients with ESRD (59% men, 71.3 ± 11.0 years, 28.5 ± 5.67 kg/m², 7 mo. to 13.5 years on hemodialysis) were recruited from four dialysis centers.

Intervention: Supervised full-body PRT (3 sets, 11 exercises, moderate intensity) was prescribed three times per week during routine hemodialysis treatment.

Outcomes & measurements: The primary outcome was brachial-ankle PWV measured via applanation tonometry. Secondary outcomes included augmentation index (AI), brachial and aortic blood pressures, progenitor cells (PCs), endothelial progenitor cells (EPCs), C-reactive protein, blood lipid profile (high-density and low-density lipoprotein cholesterol, total cholesterol, triglyceride) and anthropometrics.

Results: Non-normally distributed data were normalized using logarithmic transformation. No significant change in log-PWV was detected between control and intervention periods [mean difference = 0 (95% CI = -0.1 to 0.1); $P=0.58$]. Similarly, no significant change was noted in any of the secondary outcomes between the control and intervention periods. Post-hoc analyses limited to participants who attended $\geq 75\%$ of the PRT sessions ($n=11$) did not differ from the primary analysis.

Limitations: Low number of participants, lack of a parallel arm control group, measurement of brachial-ankle PWV rather than central arterial stiffness.

Conclusions: 12 weeks of low-to-moderate intensity intradialytic PRT did not change PWV, hemodynamic, anthropometric or hematologic measures in patients with ESRD. More research is needed to determine whether different intensities or durations of PRT can affect vascular health or other outcomes related to survival.

6.2 Introduction

Progression of chronic kidney disease is associated with an exponential increase in atherosclerotic cardiovascular disease (CVD) and associated mortality (1). CVD is the leading cause of hospitalization and death in patients with end stage renal disease (ESRD) receiving maintenance hemodialysis (2). Data suggest a 10-30 fold higher risk of CVD-related mortality versus the general population (3). As the ESRD population continues to grow (2), greater efforts must be directed toward reducing CVD morbidity and mortality in this cohort.

Progressive resistance training (PRT) is well recognized for inducing muscle anabolism, and improving physical functioning and health-related quality of life in patients with ESRD (4). Accumulating evidence from other chronically diseased cohorts suggests that PRT can also attenuate CVD risk factors [e.g., hypertension, blood lipids, visceral fat, insulin resistance, and circulating C-reactive protein (CRP)] (5-9). There is preliminary evidence that patients with ESRD can achieve such adaptations to PRT, however, data remain inconsistent, warranting further investigation (10).

Pulse wave velocity (PWV) is a measure of arterial stiffness that can be assessed non-invasively using applanation tonometry (11). Elevated PWV reflects greater arterial calcification or arteriosclerosis (i.e., lower arterial compliance) and is a strong predictor of cardiac events and CVD mortality in ESRD (12, 13) and other clinical cohorts such as non-dialysis CKD, hypertension and coronary artery disease (14). Previous studies have shown that intradialytic aerobic training can significantly reduce PWV (15). This improvement in arterial stiffness could be partially mediated by enhanced vascular repair reflected in the increased number and/or function of progenitor cells (PCs) and the more lineage committed endothelial progenitor cells (EPCs) (16, 17).

Interventions that decrease arterial stiffness (increase arterial compliance) and increase circulating EPCs may contribute to better CVD-related survival in patients with ESRD (12, 13, 18). Current evidence suggests that PRT may mitigate CVD risk in patients with ESRD by mitigating risk factors such as blood lipids (i.e. total cholesterol and triglyceride) (19), CRP (20-23), and body adiposity (19, 24). However, there has been no investigation of the effect of PRT on arterial stiffness and associated biomarkers (e.g., PCs and EPCs) in patients with ESRD. Therefore, the purpose of this study was to investigate the effect of a 12-week intradialytic PRT intervention on PWV and secondary relevant outcomes (i.e. hemodynamic, anthropometric, and hematologic). We hypothesized that 12 weeks of PRT would significantly reduce PWV, AI, and CRP, increase PCs and EPCs, and improve lipid profile.

6.3 Methods

Study Design

This study utilized a non-randomized, within-subjects crossover design comparing change over an initial 12-week control period (usual care [no exercise]; week 1-12) with a 12-week intervention period (intradialytic PRT; week 14-25). Primary and secondary outcome measures were assessed at baseline (week 0), after the control period (week 13) and after the intervention period (week 26). Post intervention testing was completed >72 hours after the final exercise session to avoid acute exercise effects. The Western Sydney University Human Research Ethics Committee (Research Code: H9651) and the Central Northern Adelaide Health Service (RAH HREC No.: 120507) approved all research procedures.

Participants and recruitment

Eligibility criteria: (1) adult aged ≥ 40 years, (2) medically stable and adequately dialyzed ($Kt/V \geq 1.2$) for greater than three months, (3) able to ambulate independently or with an assistive device for ≥ 50 m, (4) no amputation, (5) no acute or chronic medical condition that contraindicated or prevented the performance of PRT during hemodialysis treatment, (6) cognition and English language sufficient to understand research procedures and provide written informed consent, (7) sedentary (i.e., less than 120 min of moderate-intensity physical activity per week) (25), (8) no recent participation in PRT. Participants were recruited from four outpatient hemodialysis centers in South Australia. All patients were evaluated for eligibility, which involved review of the medical and clinical records, clearance from the nephrologist, and interview of the patient.

Control Period

Participants remained sedentary. They were provided usual medical and hemodialysis treatments.

Intervention Period

Participants were prescribed intradialytic PRT three times per week under the direct supervision of an exercise physiologist (26). The upper limb containing the vascular access was exercised prior to each dialysis session. The intradialytic exercises were completed during the first half of each hemodialysis session.

Table 6.1. Progression of the resistance training program

Week	Number of sets	Number of repetitions	RPE
1 – 2	3	12 – 15	12 – 13
3 – 4	3	12 – 15	13 – 14
5 – 12	3	10 – 12	14 – 15

RPE, rating of perceived exertion³¹.

A combination of PRT equipment was used, including: (i) a customized Maxim Fitness™ weight resistance machine (Hindmarsh, SA, Australia) for chest press, seated row, leg press, knee flexion and bent knee hip flexion, (ii) Thera-band™ elastic tubing (Akron, Ohio, USA) with handles (Practitioner Supplies, Clovelly Park, SA, Australia) for back extension, knee extension and bent knee hip flexion (multiples of 5 color-graded elastic tubing were used to increase resistance progressively) (27), and (iii) free weight dumbbells (Celsius™, China) for shoulder

press, biceps curl and triceps extension. Exercise volume and intensity based on rating of perceived exertion (28) is presented in Table 6.1. The duration of the training session was approximately 30 minutes. Exercises that targeted different muscle groups were alternated set-to-set.

Outcome measures

Pulse wave velocity and secondary hemodynamic outcomes

The primary outcome was brachial-ankle PWV. Secondary outcome measures included augmentation index (AI), brachial and aortic blood pressures, progenitor cells (PCs), endothelial progenitor cells (EPCs), C-reactive protein, blood lipid profile [i.e. high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride], and anthropometrics (body weight, waist circumference, body mass index). AI served as a surrogate measure of arterial stiffness (29).

To minimize the effect of fluid shifts on vascular and hemodynamic measures (30), assessments were conducted at the same time of day and on the same day of the week (mid-week non-dialysis) for the baseline and follow-up assessments (week 13 and 26) (30-32). The assessment of PWV involved electrocardiogram-gated sequential applanation tonometry (SPT-301; Millar Instruments, Houston, Texas) to acquire waveforms at the brachial and tibial arteries (SphygmoCor 7.1; AtCor, www.atcormedical.com). Aortic blood pressures and AI were estimated using radial applanation tonometry (SphygmoCor 7.1) performed on non-fistula arm using a validated and reproducible generalized transfer function (31, 33). AI is also normalized to a heart rate of 75 beats per minute (34). A single trained non-blinded operator (D.C.) tested all

participants. Participants fasted from food and caffeinated drinks for a minimum of 4 hours prior to assessment. Resting brachial blood pressure was measured after 15 min supine rest using an aneroid sphygmomanometer. PWV was derived as distance (meters)/transit time between the brachial and tibial arterial sites (seconds). Pulse pressure (PP) was derived from the difference between measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings. The heights of brachial, sternal notch and posterior tibial arterial sites were measured to determine the distance for PWV.

Anthropometric outcomes

Body Mass Index (BMI) in kg/m^2 was computed from measured height and weight. Waist circumference was measured according to standard protocol (28).

Hematological outcomes

Peripheral blood samples for PCs (CD133+CD34+) and EPCs (CD133+CD34+CD31+) were collected prior to the first dialysis session and were processed within 2 hours of being collected. Peripheral blood samples for other hematological measures were collected prior to the second dialysis session.

Blood samples were diluted 1:1 with sterile phosphate buffered saline (PBS) and mononuclear cells (MNCs) isolated via Lymphoprep™ (Axis-Shield, Oslo, Norway) density gradient centrifugation. Cells were washed in HUVE media (Media 199 (Sigma-Aldrich, MO, USA); containing 20% FCS (Hyclone, Utah, USA), 1.5% sodium bicarbonate, 2% HEPES buffer solution, Penicillin Streptomycin, sodium pyruvate (all Gibco Invitrogen, Gaithersburg, MD, USA) and non-essential amino acids (Sigma-Aldrich) prior to staining for flow cytometric analysis. Cells were blocked with 10 μ l of human FcR blocking reagent (Miltenyi Biotec,

Bergisch Gladbach, Germany). Cells were washed prior to blocking with 5µl normal mouse serum (Sigma-Aldrich) and immediately incubated with panels of mouse anti-human conjugated antibodies; anti CD14 PE-Cy7, anti CD144 FITC, anti CD34 Percp-Cy5.5, anti CD45 Amcyan, anti CD31 V450 (all BD Biosciences, Franklin Lakes, NJ, USA) and anti-CD133-PE (Miltenyi Biotec) used as per manufacturer's instructions as well as the viability dye eFlour®780 (1:1000, eBioscience, San Diego, CA, USA). The cells were then re-suspended in FACS fix (1% formaldehyde, 20g/L glucose, 5mM sodium azide, in PBS). Flow cytometric analysis was performed on a FACS ARIA II (BD Biosciences) with PCs and EPCs analyzed via FCS Express 4 (De Novo Software, Glendale, CA, USA) and recorded as percentage of MNCs.

Blood samples for CRP assay were collected in lithium heparin coated Vacuette tubes. CRP assays were analyzed using the Siemens Healthcare Diagnostics ADVIA Chemistry system (Tarrytown, NY, USA) (CV=3.8%).

Blood lipids, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides were analyzed using the Siemens Healthcare Diagnostics ADVIA Chemistry system. LDL cholesterol was calculated as $LDL-C = [Total\ Cholesterol - (Triglycerides/2.2)] - HDL-C$. The CV for total cholesterol, HDL-C and triglyceride ranged from 1.3-6.3%.

Compliance and adverse events

Compliance to PRT (%) was defined as the number of sessions attempted divided by the number offered x 100. Changes in health status, including acute illnesses, falls, changes in medication dosage and usage, visits to health care professionals and exercise-related adverse

events were documented during the control and intervention periods by means of a structured questionnaire and review of clinical notes on a weekly basis. A PRT-related adverse event was defined as any injury, impairment or medical condition persisting that could be attributed directly due to the prescribed exercise program.

Statistical analyses

There are no published data on the effects of PRT on PWV in patients with ESRD. A sample size estimate was informed by a *post hoc* computation provided by Koh *et al.* (35). Their data suggested that 36 participants per group would be needed to detect statistical significance for a clinically significant reduction of 1.0 m/s in PWV between an exercise and control group within a randomized controlled trial (RCT) (ES = 0.67; $\alpha = 0.05$ and $1-\beta = 80\%$) (35). Assuming between measures correlation of 0.5, the required sample size for a crossover design was computed as $n=20$ to detect the same effect size on PWV.

Analyses were performed using SPSS (IBM©, Version 19.0). All data were inspected visually and statistically for normality at each timepoint (weeks 0, 13, and 26). Normally distributed data were described using mean \pm standard deviation. Non-normally distributed data were log-transformed (\log^{10}) across the three timepoints prior to entry into parametric statistical models. Primary analysis incorporated a linear mixed model defining individual as the random effect with the outcome measure evaluated across three timepoints (weeks 0, 13, 26). All data were included regardless of participant compliance to the intervention according to the intention-to-treat principle ($n=22$). Each model was also adjusted for age, gender, dialysis vintage, and interactions for time by age, time by gender and time by dialysis vintage. P-values were reported for the change from week 0 to week 13 and change from week 13 to 26. In addition, the

mean difference and effect size were computed comparing the control period (week 13 – week 0) to the intervention period (week 26 – week 13). Linear univariate regression analyses were performed using pooled data to determine significant relationships between PWV and all outcome measures at baseline. In addition, regression analyses were performed to evaluate relationships between changes in PWV and changes in all outcome measures during the PRT intervention period (week 14-week 25).

6.4 Results

Participant and recruitment

Twenty-two eligible participants consented to participate and completed baseline assessment, comprising 11% of the total patients reviewed (n=195). Participant flow is presented in Figure 6.1.

Baseline characteristics

Patient characteristics for the total cohort (n=22) are presented in Table 6.2. Age ranged from 51 to 89 years and dialysis vintage ranged from 7 months to 13.5 years. The majority of participants were overweight (36.4%) or obese (27.3%). All except five participants were on one or more anti-hypertensive medications, and baseline blood pressure indicated stage 1 hypertension in the cohort (36). Half of the participants (n=11, 50%) were prescribed beta-blockers and/or calcium channel blockers. The ethnicity of the participants was pre-dominantly Caucasian (n=17, 77.3%).

Compliance and adverse events

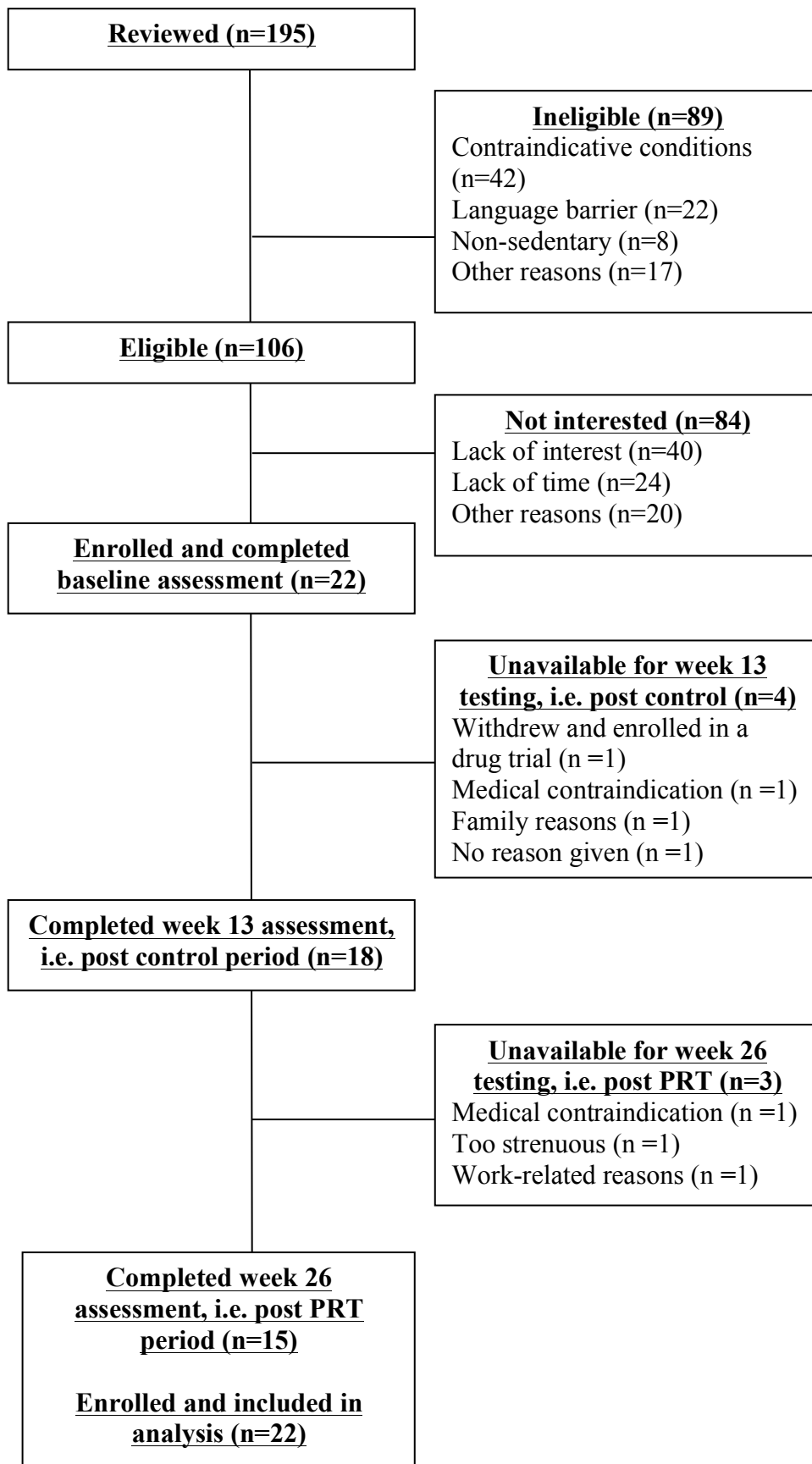
Compliance to PRT in the 18 participants who undertook the intervention was $71.2 \pm 23.3\%$. Eleven of 18 participants achieved at least 75% compliance (i.e., greater than 27 of 36 sessions attended). Three participants who refused follow-up assessment at week 26 completed less than 20% of the PRT intervention. One participant experienced dizziness during one training session while exercising during hemodialysis. Blood pressure was found to be normal, however exercise was immediately ceased. There were no other adverse events.

Table 6.2. Baseline characteristics of the total cohort (n=22)

	Total cohort
Age (years)	71.3 ± 11.0
Sex (men: women)	13:9
Ethnicity	
Caucasian, <i>n</i> (%)	17 (77.3)
Asian, <i>n</i> (%)	1 (4.5)
Aboriginal, <i>n</i> (%)	2 (9.1)
Indian, <i>n</i> (%)	2 (9.1)
Height (cm)	161.4 ± 10.4
Body weight (kg)	74.6 ± 17.9
Body Mass Index (kg/m ²)	28.5 ± 5.6
Dialysis vintage, months (range)	42.5 (7 – 163)
Systolic blood pressure at rest (mm Hg)	149 ± 24
Diastolic blood pressure at rest (mm Hg)	68 ± 9
Dialysis adequacy (Kt/V)	1.72 ± 0.26
Serum creatinine (µmol/L)	706.2 ± 141.8
Serum albumin (g/L)	35.6 ± 2.3
<u>Medications, <i>n</i> (%):</u>	
Erythropoiesis stimulating agents	18 (81.8)
Beta blockers	11 (50.0)
Calcium channel blockers	11 (50.0)
Nitrates	4 (18.2)
Angiotensin-converting enzyme inhibitors	3 (13.6)
Alpha blockers	3 (13.6)
Angiotensin II receptor blockers	1 (4.5)
Tobacco use history (<i>n</i>)	11
Etiology of kidney failure	
other, <i>n</i> (%)	12 (54.5)
diabetes, <i>n</i> (%)	7 (31.8)
hypertension, <i>n</i> (%)	2 (9.1)
glomerular diseases, <i>n</i> (%)	1 (4.5)

Data reported according to mean ± standard deviation except dialysis vintage (median value and range reported due to non-normal distribution). Dialysis adequacy (Kt/V) greater than or equal to 1.2 is considered adequate.

Figure 6.1. Participants flow



Baseline relationships

PWV was positively correlated with brachial SBP ($r=0.49$, $P=0.04$) and PP ($r=0.51$, $P=0.03$), and inversely correlated with PCs ($r=-0.68$, $P=0.045$). No other relationships were noted between PWV and other outcome measures.

Outcomes

Linear mixed model analysis results for the primary and secondary outcome measures are presented in Table 6.3.

Pulse wave velocity and secondary hemodynamic outcomes

Due to non-parametric distribution, the PWV data were normalized using logarithmic (\log_{10}) transformation. No significant change in log-PWV was detected between control and intervention periods [mean difference = 0 (95% CI = -0.1 to 0.1); $P=0.58$]. Similarly, no significant change was noted in any of the secondary hemodynamic outcomes, including AI, AI at 75bpm, and aortic and brachial blood pressures (diastolic-, systolic- and pulse pressures), between control and intervention periods (Table 6.3).

Anthropometric outcomes

No change was noted in any anthropometric outcome, including weight [mean difference = -0.95 (95% CI = -10.86 to 8.95); $P=0.30$], BMI [mean difference = -0.43 (95% CI = -7.87 to 7.01); $P=0.26$] or waist circumference [mean difference = -0.41 (95% CI = -9.81 to 8.98); $P=0.61$] between the control and intervention periods (Table 3).

Table 6.3. Primary outcome (PWV) and secondary hemodynamic measures

Outcome Measures	Week 0	Week 13	Week 26	<i>P</i> (time)	<i>P</i> (week 13 vs week 0)	<i>P</i> (week 26 vs week 13)	Mean Difference (95% CI) (Intervention - Control period)	Relative ES (95% CI) (Intervention - Control period)
Primary outcome:								
PWV (m/s)	12.3 (9.1 – 20.8)	11.5 (9.7 – 20.0)	13.0 (9.3 – 26.7)	0.70	0.45	0.58	0 (-0.1, 0.1)	0.02 (-0.61, 0.57)
Secondary outcomes:								
<u>Hemodynamic outcomes</u>								
AI (%)	34.9±12.6	33.5±13.0	33.9±16.0	0.78	0.60	0.90	1.9 (-5.9, 9.7)	0.14 (-0.45, 0.74)
AI at 75 bpm (%)	30.6±10.7	30.3±11.1	32.6±14.0	0.88	0.90	0.46	2.7 (-3.9, 9.4)	0.24 (-0.35, 0.84)
Aortic SBP (mmHg)	139±25	133±26	128±32	0.19	0.31	0.48	1 (-14, 17)	0.04 (-0.55, 0.63)
Aortic DBP (mmHg)	69±10	68±10	67±12	0.17	0.40	0.71	1 (-5, 7)	0.08 (-0.51, 0.67)
Aortic PP (mmHg)	69±23	65±23	61±28	0.22	0.39	0.40	-1 (-15, 13)	0.03 (-0.62, 0.56)
Brachial SBP (mmHg)	149±24	143±26	136±30	0.17	0.28	0.25	-1 (-17, 14)	0.05 (-0.64, 0.54)
Brachial DBP (mmHg)	68±9	67±10	66±11	0.16	0.55	0.54	-0.2 (-5.8, 5.4)	0.02 (-0.61, 0.57)
Brachial PP (mmHg)	80±22	76±23	71±26	0.16	0.32	0.28	-1 (-15, 13)	0.05 (-0.64, 0.54)
<u>Anthropometric outcomes</u>								
Weight (kg)	72.6±16.3	72.9±16.3	72.3±16.4	0.10	0.51	0.30	-0.95 (-10.86, 8.95)	-0.058 (-0.649 – 0.534)
BMI (kg/m ²)	28.2±5.8	28.4±5.9	28.1±5.9	0.10	0.37	0.26	-0.43 (-7.87, 7.01)	-0.035 (-0.626 – 0.556)

Waist circumference (cm)	99.6±14.5	99.6±14.6	99.1±14.9	0.84	0.94	0.61	-0.41 (-9.81, 8.98)	-0.026 (-0.617 – 0.565)
<u>Hematological outcomes</u>								
Progenitor cells (%)	0.044±0.042	0.054±0.033	0.050±0.038	0.77	0.38	0.68	-0.014 (-0.037, 0.009)	0.36 (-0.96, 0.23)
EPC (%)	0.025±0.033	0.044±0.028	0.039±0.033	0.34	0.047	0.53	-0.024 (-0.043, 0.005)	0.77 (-1.38, -0.16)
CRP (mg/L)	4.2 (2.2 – 15.7)	5.0 (1.6 – 9.3)	7.4 (3.6 – 15.5)	0.92	0.08	0.057	0.49 (0.13, 0.86)	0.8 (0.19, 1.42)
HDL-C (mmol/l)	1.2±0.3	1.1±0.3	1.1±0.3	0.11	0.34	0.94	0.007 (-0.24, 0.25)	0.02 (-0.81, 0.86)
LDL-C (mmol/L)	2.2±0.9	2.1±0.9	2.1±1.0	0.71	0.21	0.64	0.37 (-0.54, 1.29)	0.35 (-0.49, 1.19)
Cholesterol (mmol/L)	4.3±0.9	4.1±0.9	4.1±1.0	0.13	0.30	0.81	0.39 (-0.63, 1.40)	0.32 (-0.51, 1.17)
Triglyceride (mmol/L)	1.6 (1.3 – 2.3)	1.6 (1.3 – 2)	1.4 (1.05 – 2.1)	0.08	0.61	0.31	-0.03 (-0.23, 0.17)	-0.12 (-0.96, 0.71)

Log PWV, logarithm-transformed pulse wave velocity; AI, augmentation index; AI at 75 bpm, augmentation index normalised to a heart rate of 75 beats per minute; ES, effect size; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; EPC, endothelial progenitor cells; Log CRP, logarithm-transformed C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Data reported according to mean ± standard deviation except non-normal distributed data [median (range)].

The mean difference expresses the mean difference in the outcome between the control and intervention periods. The relative effect size is the mean difference between the two periods divided by the pooled standard deviation of the outcome at baseline among participants.

Hematological outcomes

Due to non-normal distribution, both CRP and triglycerides were normalized using logarithmic (\log_{10}) transformation prior to parametric statistical analyses. No change was noted in any of the hematological measures, including PCs [mean difference = -0.014 (95% CI = -0.037 to 0.009); $P=0.68$], EPCs [mean difference = -0.024 (95% CI = -0.043 to 0.005); $P=0.53$], log CRP [mean difference = 0.49 (95% CI = 0.13 to 0.86); $P=0.06$], HDL-C, LDL-C, total cholesterol, and log triglyceride between the control and intervention periods (Table 6.3).

Associations of Adaptation of PWV

No relationships were noted between change in PWV and changes in any other outcome measures.

Post hoc analyses

Post-hoc analyses were conducted to evaluate the effect of adherence on adaptation. Linear mixed model analyses were computed for all outcome measures using data from participants who attended $\geq 75\%$ of the PRT sessions ($n=11$). The findings of these analyses remained essentially unchanged from the primary analysis.

6.5 Discussion

To our knowledge, this is the first study to assess the effect of a chronic PRT intervention on PWV and secondary outcomes (i.e., hemodynamic, anthropometric, and hematologic) potentially contributing as mechanisms to the adaptation of arterial stiffness in patients with ESRD undergoing maintenance hemodialysis. Contrary to our hypotheses, the results indicate that a 12-week low-to-moderate intensity intradialytic PRT program does not significantly change PWV or associated biomarkers of CVD risk. These findings have implications for the development of future clinical trials investigating the cardiovascular benefits of exercise training in ESRD.

To date, three clinical trials have examined the effects of aerobic training on the arterial stiffness measures in hemodialysis patients (15, 35, 37). In contrast to the current study, Toussaint *et al.* (15) observed a significant reduction in PWV ($P=0.008$) and trend toward significant improvement in AI ($P=0.062$) after three months of intradialytic cycling. Similarly, Mustata *et al.* (37) in an uncontrolled trial of 11 patients reported a significant reduction in AI and PP secondary to 12 weeks of treadmill and/or recumbent exercise cycling during non-dialysis time. Koh *et al.* (35) compared the outcomes of hemodialysis patients prescribed intradialytic cycling, a home-based walking program or usual care and showed no significant change in PWV and AI in either of the exercising groups. The lack of adaptation in that study could be due to its lower intensity (RPE of 12-13), lower work or shorter duration sessions compared to the intervention prescribed by Toussaint *et al.* (15) (35 kilocalories versus 70 kilocalories) or Mustata *et al.* (37) (60 to 80% maximal heart rate). Therefore, the results of the existing research may collectively suggest that aerobic training at a sufficient intensity level and or volume may significantly improve PWV and other measures of arterial stiffness.

Two systematic reviews suggest that PRT is not as effective as aerobic training in improving measures of arterial stiffness (i.e., PWV or AI) (38, 39). Ashor *et al* (38) conducted a meta-analysis of 42 RCTs enrolling 1627 healthy and chronically-diseased participants found that isolated aerobic training significantly reduced PWV [weighted mean difference = -0.63 m/s (95% CI: -0.90, -0.35); $P < 0.01$] and AI [weighted mean difference = -2.63% (95% CI: -5.25 to -0.02); $P = 0.05$], however isolated PRT did not change these measures. Interestingly, Miyachi *et al.* (39) conducted a systematic review of 8 RCTs in 193 participants who were apparently healthy or had stage 1 hypertension and determined that high-intensity PRT (>70% 1RM) actually increased arterial stiffness (carotid β index or PWV). However, no effect on arterial stiffness was noted with moderate intensity (40-70% 1RM) PRT.

The findings of the present study appear to be congruent with the findings of Ashor *et al.* (38) and the findings for moderate intensity PRT elucidated by Miyachi *et al.* (39). We found no evidence of a dose-response effect on arterial stiffness; i.e., participants who attended >75% of exercise sessions did not achieve results which differed from our primary analyses of the total cohort. Similarly, the meta-analysis by Ashor *et al.* (38) documented no relationship between PRT intervention characteristics (i.e. absolute and relative intensity, exercise duration and frequency) on changes in PWV. Hence, the empirical data suggest that PRT does not improve arterial stiffness.

The vascular endothelium secretes vasoactive substances to regulate vascular smooth muscle tone and therefore partially mediates changes in arterial stiffness (40, 41). Recent data suggest that exercise-induced shear stress is the mechanism by which endothelial function is improved (42). However, different modalities of exercise can elicit different patterns of shear stress (43). Aerobic exercise (e.g., running, cycling) typically involves rhythmic movements that activate a large number of muscle groups. This form of exercise has been shown to substantially

increase both ante-grade and retrograde blood flow, while PRT exercises targeting specific muscle groups (e.g., arm flexors) do not produce such effects (44, 45). One study has shown that 8 weeks of forearm exercise consisting of squeezing a rubber ring for 30 minutes daily can induce local changes in the radial artery in endothelial-dependent vasodilation. However, such exercise may more closely resemble aerobic training than PRT due to its rhythmical nature.

The null effect of PRT on arterial stiffness and associated hemodynamic measures was accompanied by no change in CD34+CD133+ PCs or the more vascular committed CD34+CD133+CD31+ EPCs. Patients with ESRD have lower number of circulating EPCs, lower endothelial colony forming units (e-CFU) and impaired EPCs mobilization (46). Higher quantities of EPCs are required for the maintenance and repair process of the damaged endothelium (47-50). Only one exercise study to date has investigated its effect on PCs and EPCs in patients with ESRD. Manfredini *et al.* (16) conducted a controlled trial of a 6-month moderate intensity aerobic training intervention. The exercise protocol consisted of two 10-minute walking sessions per day at 50% of the patient's maximum treadmill speed, performed at home on at least three non-dialysis days per week. No difference was found in circulating PCs (CD34+), EPCs (CD34+CD133+VEGFR2+) and e-CFU post intervention between the exercise group (n=14) and control group (n=8). The lack of change of circulating EPCs numbers in the current study and in the aerobic training study by Manfredini *et al* study (16) may be due to the uremia associated with ESRD, as uremia has been shown to increase EPCs apoptosis and reduce progenitor cells differentiation into EPCs (51).

The lack of change in other hematological and anthropometric measures, including log-CRP, HDL-C, LDL-C, log-triglyceride, weight, BMI and waist circumference is consistent with the null effect the intervention had on arterial stiffness. These secondary hematological and anthropometric measures are known to contribute to arterial stiffness, while exercise exerts its

benefits on vascular health in other cohorts partially by altering these factors (52-55). The effect of PRT on these outcome measures in patients with ESRD remains inconsistent (22, 56-60).

Limitations of this study include low number of participants and the lack of a parallel arm control group. No sample size can be estimated from post-hoc analysis for change in PWV between intervention and control period as there is no discernible change in PWV (relative ES = 0) in the current study. However, post hoc power calculations indicated that it would have required a sample size of 138 for the small ES detected in AI to be significant with $\beta=0.2$ and $\alpha=0.05$. Thus, it is possible that a Type II error may have contributed to the lack of statistical significance in our sample, at least for this secondary estimate of central aortic stiffness which was measured by radial artery applanation tonometry. Thus, future studies powered for small ESs would be needed to determine more definitively whether PRT has the ability to maintain or decrease arterial stiffness in patients with ESRD, using more precise measures of arterial stiffness than the current study.

An important limitation relates to the specific assessment of PWV in this study. Previous studies (61, 62) have only established central arterial stiffness (aortic PWV) as a strong independent predictor of mortality in ESRD. As the current study measured brachial-ankle PWV, it is uncertain whether aortic arterial stiffness was unchanged. The PWV measured in the current study is considerably faster than previous aerobic training studies (15, 35, 37), making it unlikely that this was solely due to peripheral method of measuring arterial stiffness (63). The current cohort may thus have had more advanced arterial stiffness than previous cohorts, limiting the potential for adaptation to exercise. Arterial stiffening is also associated with ageing (64). The current cohort was elderly and comparatively older than most previous exercise studies in this population (23, 35, 37, 59).

Although PRT can result in increased arterial stiffness in some younger healthy cohorts, this is not evident in middle-aged, older cohorts (39), including clinical cohorts such as type 2 diabetes (65) and chronic heart failure patients (66). In young cohorts, the magnitude of increase in arterial stiffness after PRT is also unlikely to be clinically adverse as the increase still leaves them in the normal range (39).

In conclusion, the current findings suggest that appropriately screened, older patients with ESRD can safely participate in a supervised PRT without worsening arterial stiffness. More research is needed to determine if different intensities of PRT or longer training durations can alter vascular health and other outcomes related to survival.

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Chapter 7

Conclusion

Conclusion and Summary

The results of this thesis have extended the current understanding in several areas. While a few studies have reported the effects of aerobic exercise training on arterial stiffness and other cardiovascular outcomes in patients with ESRD, there is limited research evaluating the effects of intradialytic PRT in this population group. Conventional hemodialysis centers are not designed with space for commercial exercise equipment. Although previous clinical trials were successful in implementing exercise training during hemodialysis, they are primarily aerobic exercise or light resistance exercise. Rudimentary resistance exercise equipment was often used which had limited resistance load for continual positive physiological adaptations. Few studies had endeavored to develop, test and report the feasibility of resistance exercise equipment purpose-built for delivering a comprehensive, intradialytic PRT in conventional hemodialysis setting.

This thesis sought to fill these gaps in the literature by first conducting a systematic review (Chapter 4) and meta-analysis (Appendix 2) to determine the most efficacious PRT programming and expected PRT benefits on physiological, functional and psychological outcomes. The main findings of this review are that PRT can increase lower body muscular strength, muscle mass, physical functioning and HRQoL whilst its effects on other important outcome measures remain inconsistent. The following recommendations for future clinical trials were also suggested. Future clinical trials should describe thoroughly exercise programming including frequency, intensity, modality, supervision and progression to allow detailed synthesis of results. The few studies of moderate to high intensity PRT interventions which maximize muscle hypertrophy seemed to also mediate cardiovascular disease risk factors such as inflammation, insulin sensitivity, body fat and dyslipidemia. It is therefore recommended that future trials should ascertain concurrent, dose-response effects of PRT on cardiovascular health

and disease risk factors. More PRT intervention should also target both upper and lower body muscle groups to maximise its physiological benefits.

This research program followed some of these recommendations by including the development of a purpose-built training device and evaluating the effects of an intradialytic PRT intervention delivered using the device on cardiovascular, functional and psychological outcomes in patients with ESRD. The research demonstrates that it is feasible to deliver PRT in a conventional hemodialysis setting with a purpose-built training device, resulting in improved muscular strength and HRQoL (Chapter 5). The research has also found that upper body exercises can be incorporated safely in a hemodialysis setting with proper supervision by an exercise physiologist. The intervention was conducted in 3 different hemodialysis centers and no serious adverse event was reported as a consequence of PRT.

Although the average age of the cohort is older than previous PRT studies, no serious adverse events occurred in the current trial. This indicates that, with appropriate screening, even patients who are older but willing to participate can safely perform both upper and lower body exercises prior to or during dialysis with proper supervision. As hemodialysis patients may either have to wait for a lengthy period or have low chance of renal transplants, the improvements in HRQoL and lower body strength evident in the current intervention are important findings and does justify the incorporation of PRT in clinical care. Nephrologists, nurses and exercise physiologists need to work closer to design in-center exercise program and should consider the use of exercise equipment purpose-built for hemodialysis setting to increase the ease of prescribing quality PRT.

Lastly, this research also showed null effect of 12 weeks of moderate PRT on arterial stiffness measures hemodynamic, anthropometric or hematologic measures in patients with ESRD. This is the first study to investigate the effect of PRT on arterial stiffness and endothelial progenitor cells in ESRD, and Type II error is likely to contribute to our measure of AI. The null effect on arterial stiffness measures and endothelial progenitor cells should therefore be interpreted with reservations. As hemodialysis centers have limited number of patients that are willing and eligible to participate, a future RCT involving multiple centers will be necessary to generate bigger study cohort.

New studies need to also investigate whether isolated PRT or combined with aerobic training can affect these cardiovascular outcomes in patients with less severe chronic kidney disease (stage 1 to 4) as they may have better chance of improvement due to less severe renal-specific cardiovascular risk factors. Future research should also determine whether different intensities and longer durations of PRT can affect vascular health or other outcomes related to survival.

In conclusion, the most significant contribution of this research is the first to develop and utilize a portable training device for both upper and lower body exercises in a comprehensive intradialytic PRT program. Only two studies that used novel resistance training devices were limited to lower body exercises. This is also the first trial to assess the effect of intradialytic PRT on arterial stiffness and endothelial progenitor cells in patients with ESRD. In conclusion, the intervention has expanded the conventional mode of exercise prescription in the hemodialysis setting, reproduced common benefits of PRT and investigated novel cardiovascular effects of PRT in ESRD.

Appendix

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Appendix 1. Publication – Resistance Training in Chronic Renal Failure

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Introduction

Chronic kidney disease (CKD), also known as chronic renal failure, is an irreversible disease characterized by the progressive loss of kidney function over time, usually a period of months to years (Eckardt, Berns, Rocco, & Kasiske, 2009; Levey et al., 2005). Prevalence data for CKD are difficult to ascertain given that the early stages of the disease process are typically asymptomatic (Dasmahapatra et al., 2011), and given inconsistencies in diagnostic and classification systems (Glasscock & Winearls, 2008). However, recent data from the *National Health and Nutrition Examination Survey* (NHANES) suggest that 13.1% of adults (aged >20 years) living in the United States had Stage 1 to 4 CKD in 2004 (Coresh et al., 2007). More recent estimates by the *United States Renal Data System* suggest that 15.1% of the adult population in the United States has CKD (USRDS, 2011).

The prevalence of CKD has increased gradually over the past several decades within the United States (Coresh et al., 2007) and globally (El Nahas & Bello, 2005) and these trends are expected to continue (El Nahas & Bello, 2005; Lysaght, 2002). Global estimates suggest that the prevalence of CKD is threatening to reach epidemic proportions in both developed and developing countries, and that much of the burden can be attributed to the obesity-type 2 diabetes pandemic (El Nahas & Bello, 2005). Certain ethnic populations are severely affected by late-stage CKD. These cohorts include African Americans (Klag et al., 1997), Hispanic Americans (Lora et al., 2009) and the aboriginal people of Canada (Yeates & Tonelli, 2010), the United States (Narva, 2008), New Zealand (Collins, 2010) and Australia (Australia and New Zealand

Dialysis and Transplant Registry, 2011), amongst others. The prevention and treatment of CKD globally will become a major challenge in the coming decades (El Nahas & Bello, 2005).

Diabetes and hypertension are currently the leading causes of CKD accounting for almost 70% of cases (Bakris, Ritz, & On behalf of the World Kidney Day Steering, 2009). Other causes include glomerulonephritis, IgA nephropathy, polycystic kidney disease, analgesic (aspirin, ibuprofen, and paracetamol) use, systemic lupus erythematosus, benign prostate hyperplasia, HIV infection, amyloidosis, kidney infections, kidney stones, sickle cell disease, heroin use, and certain cancers (K/DOQI, 2002). The etiology of CKD is influenced by infectious diseases and genetic predisposition only in a minority of cases (e.g. polycystic kidney disease, HIV infection), whilst the majority of cases are heavily influenced by lifestyle factors. Physical inactivity, cigarette smoking and associated diseases (e.g. obesity, hypertension, dyslipidemia, diabetes) are consistently recognized as major modifiable risk factors for CKD (Hallan et al., 2006; White et al., 2011).

Individuals with a diagnosis of CKD are at significantly elevated risk of cardiovascular and all cause mortality versus healthy peers (Tonelli et al., 2006). Cardiovascular disease remains the leading cause of death in this population and the risk of cardiovascular mortality increases as kidney function declines (Sarnak et al., 2003). Notably, mortality rates due to cardiovascular disease have been reported to be 10 to 30 times higher in dialysis-dependent CKD patients than in the general population (Sarnak et al., 2003).

Diagnosis and classification

Healthy kidneys filter approximately 170 L of blood and process 1.5 L of urine each day (How Kidneys Work, 2012). Similar to the lungs, the kidneys can be considered “overbuilt” in

that the kidneys can incur tremendous damage and still sustain life without any adverse effects. For example, human beings can live normal, healthy lives with just a single kidney and have a life expectancy no different to that of the general population (Ibrahim et al., 2009).

CKD is defined according to the presence or absence of kidney damage and the level of kidney function, regardless of disease etiology (K/DOQI, 2002). CKD presents with no or few symptoms until the advanced stages (Dasmahapatra et al., 2011; K/DOQI, 2002). Therefore, diagnosis can only be undertaken *via* laboratory tests, including urinalysis, blood tests, imaging tests and kidney biopsy (K/DOQI, 2002). Each diagnostic method has limitations and therefore multiple methods are typically used (K/DOQI, 2002). However, definitive diagnosis is based on biopsy or imaging studies (K/DOQI, 2002). The pathophysiology of CKD depends on the causative factors. Vascular changes that occur with disease progression include ischemia and stenosis of the small and large vessels of the kidney. Damage to the glomeruli and renal tubules within the kidney may also underlie CKD progression.

Urinalysis can be used to detect the presence of urine casts and crystals (K/DOQI, 2002). In addition, the urine is analyzed for total protein, albumin, urea nitrogen and creatinine concentrations, measures that are all elevated in CKD. The amount of creatinine and urea in the urine serve as markers of renal function and can be used to compute the glomerular filtration rate (GFR). The *Kidney Disease Outcome Quality Initiative* (K/DOQI) has classified the severity (progression) of kidney disease by the decline GFR (Table 1) (K/DOQI, 2002). The GFR is widely accepted as the best overall measure of kidney function (K/DOQI, 2002).

However, it should be noted that glomerular injury in the early stages of CKD may induce compensatory glomerular hypertrophy, hypertension and hyperfiltration, reflected by an increase of GFR (K/DOQI, 2002). However, this rise of GFR is typically followed by the progressive decline of GFR if preventative measures are not undertaken. Hyperfiltration has often been noted in individuals with diabetes mellitus, polycystic kidney disease, hypertension and obesity

(Brenner, Lawler, & Mackenzie, 1996; Helal, Fick-Brosnahan, Reed-Gitomer, & Schrier, 2012; Palatini, 2012)

In Stage 4 CKD (GFR=15-29 mL/min/1.73 m²), the patient is required to prepare for kidney replacement therapy, including hemodialysis, peritoneal dialysis or kidney transplant. Stage 5 CKD (GFR<15-mL/min/1.73 m²) is also known as end-stage renal disease (ESRD) or end-stage kidney disease. In Stage 5, the kidneys can no longer function at a level to sustain life (K/DOQI, 2002). Hence, individuals with ESRD are dialysis-dependent for the remainder of their lifetime, or until a successful kidney transplant (K/DOQI, 2002).

Conventional hemodialysis treatment

Over 91% of patients diagnosed with ESRD will undertake hemodialysis treatment, while 6% undertake peritoneal dialysis, and only 2% receive a transplant (USRDS, 2011). Failure to undertake dialysis therapy in patients with Stage 5 CKD will result in imminent death (Galla, 2000). Conventional hemodialysis treatment is typically received three times per week for approximately 3–5 hours per treatment at an outpatient clinic. Specialist nursing staff is involved in administering the dialysis sessions. Alternatives to conventional hemodialysis include daily hemodialysis treatment or nocturnal hemodialysis, which are both typically administered by the patient and/or a trained care provider at home. During conventional hemodialysis, blood is continually drawn out of the body at a rate of 200-400 mL/min to the dialysis machine where it is filtered and then returned. The entire blood volume of the patient (approximately 5L) circulates through the machine every 15 minutes. Sodium bicarbonate is often administered during hemodialysis to correct blood acidity. Recombinant human erythropoietin may be administered to correct anemia. Common side effects of hemodialysis treatment include hypotension, fatigue, chest pains, leg-cramps, nausea and headaches. Such symptoms may occur during treatment and may persist post treatment. Hemodialysis patients are typically older and suffer from many

comorbid conditions and therefore medication use is often high. Depression is a common comorbidity in this patient population.

Resistance training for the primary prevention of CKD

Interventions for the primary prevention of CKD must target such risk factors as inactivity, overweight-obesity, insulin resistance, diabetes, hypertension, dyslipidemia cigarette smoking, and the low-quality westernized diet. Scientific investigations have shown that RT prescribed in isolation can reverse overweight-obesity (Tresierras & Balady, 2009), type 2 diabetes (Sigal et al., 2007; Sukala, Page, & Cheema, 2012; Tresieras & Balady, 2009; Willey & Fiatarone-Singh, 2003) and hypertension (Cornelissen, Fagard, Coeckelberghs, & Vanhees, 2011; Fagard, 2006; Moraes et al., 2012). Hence, interventions such as RT have the potential to prevent CKD and hence drastically mitigate the rising incidence of CRF globally (El Nahas & Bello, 2005).

Resistance training in CKD and ESRD

Exercise training has been investigated in CKD since the late 1970's. Most of these investigations have involved hemodialysis patients, and have prescribed aerobic training in isolation or in combination with light to moderate strength training (Cheema & Fiatarone Singh, 2005; Johansen, 2007; Johansen & Painter, 2012). Investigations that have prescribed RT in isolation have all been published after the year 2000 (Balakrishnan et al., 2010; Castaneda et al., 2004; Castaneda et al., 2001; Cheema et al., 2007a, 2007b, 2011; Headley et al., 2002; Heiwe, Clyne, Tollback, & Borg, 2005; Heiwe, Tollback, & Clyne, 2001; Kopple et al., 2007; Leaf, Macrae, Grant, & Kraut, 2003; Nindl et al., 2004; Oder, Teodorescu, & Uribarri, 2003; Rus, Ponikvar, Kenda, & Buturovic-Ponikvar, 2003). Likewise, the majority of these studies have

enrolled hemodialysis patients (Cheema et al., 2007a, 2007b, 2011; Chen et al., 2010; Headley et al., 2002; Johansen et al., 2006; Kopple et al., 2007; Majchrzak, Pupim, Flakoll, & Ikizler, 2008; Nindl et al., 2004; Oder et al., 2003; Rus et al., 2003), while only a few trials have enrolled pre-dialysis patients (Balakrishnan et al., 2010; Castaneda et al., 2004; Castaneda et al., 2001; Heiwe et al., 2005; Heiwe et al., 2001; Leaf et al., 2003). We are aware of no studies that have prescribed RT in patients receiving peritoneal dialysis or kidney transplants.

Research of the therapeutic potential of RT in patients with CKD is in its early stages, and many research questions remain to be answered. Nevertheless, the studies published to date, which have prescribed RT in conventional fitness or rehabilitation settings, as well as during hemodialysis treatment, have largely been of good quality (Balakrishnan et al., 2010; Castaneda et al., 2004; Castaneda et al., 2001; Cheema et al., 2007a, 2007b, 2011; Chen et al., 2010; Johansen et al., 2006; Kopple et al., 2007) and have provided convincing evidence that RT is safe and can induce a broad spectrum of physiological, functional and psychological adaptations that are particularly important for patients with CKD and ESRD.

Kidney function

RT has been proven effective in targeting the main metabolic risk factors contributing to kidney damage (e.g. hypertension, type 2 diabetes, dyslipidemia, obesity, etc.) (Cornelissen et al., 2011; Fagard, 2006; Moraes et al., 2012; Sigal et al., 2007; Sukala et al., 2012; Thomas, Elliott, & Naughton, 2006; Treserras & Balady, 2009; Willey & Fiatarone-Singh, 2003). Therefore, it is highly likely that RT can also play a significant role in slowing disease progression in those already diagnosed with the disease. Interventions that induce fat loss may be particularly important for this purpose. Many trials have in patients with CKD shown that weight loss induced *via* hypocaloric diet, bariatric surgery, drugs, exercise, or lifestyle modification can reduce proteinuria and albuminuria, which indicate improved renal function (Afshinnia, Wilt,

Duval, Esmaeili, & Ibrahim, 2010; Navaneethan et al., 2009). Weight loss can also normalize the GFR in overweight and obese individuals with glomerular hyperfiltration (Chagnac et al., 2003; Navaneethan et al., 2009; Navarro-Diaz et al., 2006). There is substantial evidence that regular RT can increase total fat-free mass and resting metabolic rate contributing to the mobilization/utilization of visceral and subcutaneous adipose tissue and thereby reduce whole body adiposity (Tresierras & Balady, 2009). Hence, RT may potentially reduce proteinuria and albuminuria in individuals with CKD by inducing favorable shifts in body composition. Trials are presently required to test this hypothesis.

There is currently no consensus regarding the effect of preventative therapies on the GFR. The data suggest that reducing hypertension is particularly important for slowing CKD progression (Ruggenti et al., 2008; Tresieras & Balady, 2009). Some studies have actually shown that the GFR in patients with CKD can be increased with aerobic training interventions involving cycling or swimming (Pechter et al., 2003; Straznicky et al., 2011; Toyama, Sugiyama, Oka, Sumida, & Ogawa, 2010). However, the findings are not always consistent (Boyce et al., 1997).

To our knowledge, only one trial has reported on the effect of RT on renal function to date. Castaneda *et al.* (2001) conducted a randomized controlled trial that enrolled 26 patients with pre-dialysis CKD (i.e. Stage 3-4). All 26 participants (aged >50 years) adhered to a protein-restricted diet (0.6g/kg/day) during the trial. Protein restriction is typically prescribed for slowing disease progression (Bellizzi et al., 2007). Fourteen of the participants were assigned to a 12-week RT program while twelve participants received sham training (unloaded exercises). RT was prescribed three sessions per week and involved five exercises (chest press, leg press, lat pull-down, knee extension and knee flexion) performed for three sets at 80% of 1RM. The training loads were adjusted with strength adaptation. At the end of the 12-week intervention, the RT group experienced a statistically significant increase in the GFR from baseline (+1.18

mL/min/1.73 m²) versus the sham exercise group (-1.62 mL/min/1.73 m²; p=0.046). The improvement of GFR was also reflected by a trend toward reduced urinary creatinine concentration (p=0.074).

At present, the mechanisms underlying the RT or aerobic exercise-induced improvement of GFR (Castaneda et al., 2001; Pechter et al., 2003; Straznicky et al., 2011; Toyama et al., 2010) are not known; however, the reduction of sympathetic vasoconstrictor activity and metabolic risk factors (e.g. obesity, hypertension, insulin resistance) and improved endothelial function may be implicated (Perticone et al., 2010; Straznicky et al., 2011). Large-scale RCTs are required to confirm or refute the findings of Castaneda *et al.* (2001), and elucidate the physiological mechanisms contributing to the improvement of GFR with RT. Trials are also needed to determine the clinical significance of improved GFR in Stage 4 CKD. It is generally accepted that Stages 3-4 CKD progresses to ESRD (The Remission Clinic approach to halt the progression of kidney disease, 2011), however, it is possible that this deterioration can be delayed or even prevented with RT and other robust forms of exercise training.

Skeletal muscle wasting and inflammation

Skeletal muscle wasting, also called protein-energy malnutrition, is common in the latter stages of CKD (i.e. Stages 3 to 5) (Fouque et al., 2008; Kopple, 1999; Workeneh & Mitch, 2010). Factors such as acidosis (Caso & Garlick, 2005), co-morbid illnesses, corticosteroid usage, aging, oxidative stress, dialysis treatment (Raj et al., 2004), and very low levels of physical activity can all contribute to the loss and atrophy of muscle fibers in this cohort (Diesel et al., 1993; E. Kouidi et al., 1998). Low anabolic gene expression has been noted to underlie the muscle wasting observed in ESRD (Kopple et al., 2007). Muscle wasting can occur despite adequate nutritional intake (Rajan & Mitch, 2008) and is associated with an array of physiological consequences including insulin resistance and chronic inflammation (Price, Gooch, Donaldson, & Roberts-

Wilson, 2010; Rajan & Mitch, 2008). Patients with CKD and ESRD often suffer from low-grade inflammation reflected by chronic, two- to four-fold elevations of circulating pro-inflammatory cytokines including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α), amongst others (Avesani et al., 2006; Carrero, Yilmaz, Lindholm, & Stenvinkel, 2008; Kalantar-Zadeh, 2006, 2007; Kalantar-Zadeh, Ikizler, Block, Avram, & Kopple, 2003). Numerous investigations have shown that muscle wasting and inflammation, also termed the “malnutrition-inflammation complex”, are significant predictors of mortality in this cohort (Desmeules et al., 2004; K Kalantar-Zadeh, 2006; Shlipak et al., 2005; Wanner & Metzger, 2002).

Recent evidence suggests that RT can counteract muscle wasting and inflammation in CKD and ESRD. Castaneda *et al.* (2001) documented a significant increase in total body potassium ($p=0.014$), type I and type II muscle fiber cross-sectional area (CSA) ($p=0.031$ and $p=0.045$, respectively), serum prealbumin ($p=0.050$), leucine oxidation ($p=0.046$) and trend toward increased mid-thigh CSA ($p=0.113$) in participants prescribed 12 weeks of RT versus sham exercise. The RT group also maintained body weight while the sham exercise group reduced body weight ($p=0.049$). These adaptations are clinically relevant as they collectively indicate a reversal of skeletal muscle wasting despite a low protein diet. A subsequent report by Castaneda and colleagues revealed that the anabolic effect was accompanied by reduced inflammation, reflected by reductions of CRP and IL-6 (Castaneda et al., 2004). Moreover, the RT program elicited an increase in skeletal muscle mitochondrial DNA (Balakrishnan et al., 2010). This is an important adaptation given that mitochondrial dysfunction is common in CKD (Granata et al., 2009) and that associated deficits in energy metabolism contribute to mortality (Sietsema, Amato, Adler, & Brass, 2004). In contrast to these findings, a study by Heiwe *et al.* (2005) found no significant change in type I, type IIa, or type IIb CSA, despite improvements in 1RM, in 12 elderly pre-dialysis ($GFR \leq 25$ ml/min) patients prescribed 12 weeks of RT. Notably,

the RT regimen in this study involved only knee extensor exercises at a low intensity (60% of 1RM) (Table 2).

Three recent randomized controlled trials have demonstrated that RT can reduce or reverse muscle wasting and inflammatory markers in patients with ESRD receiving hemodialysis treatment (Cheema et al., 2007a, 2007b; Kopple et al., 2007; Johansen et al., 2006). Cheema *et al.* (B Cheema et al., 2007a, 2007b) evaluated the effect of a supervised RT program prescribed three sessions per week during routine hemodialysis treatment in 49 patients with ESRD. The regimen has been fully detailed in a recent article (Cheema et al., 2006). The limb containing the vascular access was exercised just prior to the dialysis session while all other exercises were performed while the patient was in a seated or supine position receiving dialysis. During each RT session, two sets of 8 repetitions of 10 exercises targeting the major muscle groups of the upper and lower extremities were performed at a rating of perceived exertion of 15-17/20 (“hard” to “very hard”). Upper body exercises performed using free-weight dumbbells included the shoulder press, side shoulder raise, triceps extension, biceps curl and external shoulder rotation. Lower body exercises, performed using weighted ankle cuffs included seated knee extension, supine hip flexion, supine hip abduction, and supine straight-legged raise. Seated hamstring curls were performed using Thera-Band tubing (Akron, Ohio, USA) attached to a fixed position on the weight trolley. Abdominal musculature was targeted with bilateral leg raises in a supine position or bilateral leg lifts in a seated position, depending on subject preference and level of ability. The loading of exercises was progressed appropriately with strength adaptation. After 12 weeks, participants randomized to the intradialytic RT program (n=24) experienced statistically significant improvements in mid-thigh muscle attenuation and clinically significant improvements in mid-thigh muscle CSA, evaluated *via* computed tomography, as compared to those randomized to the wait-list control group (n=25) (Cheema et al., 2007a). This improvement of muscle quality and quantity was accompanied by the significant improvement of

anthropometric measures (e.g. increases in BMI, mid-thigh and mid-arm circumferences) and the reduction of the inflammatory marker CRP (Cheema et al., 2007a). Notably, the intradialytic RT regimen did not change other circulating cytokine concentrations including tumor necrosis factor-alpha, interleukin-1b, interleukin-6, interleukin-8, interleukin-10, and interleukin-12 (B Cheema et al., 2011). The reduction of CRP has been noted in other additional trials prescribing 8 weeks of intradialytic RT (Afshar, Shegarfy, Shavandi, & Sanavi, 2010) and 12 weeks of RT during non-dialysis time (Nindl et al., 2004). This is an important finding given the morbidity and mortality associated with elevations of CRP in ESRD (Shlipak et al., 2005). Cheema *et al.* (Cheema et al., 2007b) have also noted that a longer duration of intradialytic RT can induce greater gains in muscle CSA.

Only a few additional randomized controlled trial has investigated the myogenic potential of RT prescribed during hemodialysis treatment (Johansen et al., 2006; Chen et al., 2010) Johansen *et al.* (2006) conducted a 2 x 2 factorial RCT of intradialytic RT and double-blind weekly anabolic steroid (nandrolone decanoate) or placebo injections in 79 patients with ESRD. Patients randomized to the RT intervention performed five lower body exercises using ankle weights (knee extension, hip flexion, hip abduction, plantarflexion and dorsiflexion) during thrice-weekly dialysis. Two to three sets of 10 repetitions of each exercise were performed progressing from 60% of 3RM. Training loads were increased with strength adaptation. After 12 weeks, quadriceps muscle CSA evaluated via MRI increased in the patients assigned to both RT + placebo ($p=0.02$) and RT + nandrolone ($p<0.0001$) versus control. The RT intervention did not improve total lean body mass, evaluated via DEXA, perhaps due to the fact that RT targeted only the lower extremities. However, using a similar intervention, Chen *et al.* (2010) did note significant increases in leg and whole body fat-free mass and significant reductions in whole body fat mass after approximately six months of low-intensity lower-body intradialytic RT.

To date, there has been limited exploration of the subcellular mechanisms that contribute to muscular hypertrophy in patients with ESRD. Kopple *et al.*(2007) investigated changes in anabolic and catabolic gene expression in 80 patients with ESRD randomized to four groups: (1) aerobic training, (2) RT, (3) aerobic + RT, and (4) control. All training sessions were administered three times per week for 21 weeks. The isolated RT group performed four lower body exercises (leg extension, leg curl, leg press and calf extension) three times per week immediately preceding each dialysis session. One set of 12-15 repetitions at 70% of 5-RM was performed during the first four weeks of intervention. The intervention was then systematically progressed, as tolerated, up to 3 sets of 6-8 repetitions of 80% of re-assessed 5-RM. Investigation of vastus lateralis biopsy specimens obtained from 15 patients in the RT group revealed significant increases in IGF-IEa mRNA and IGF-I protein from pre to post training. Additional anabolic genes, including IGF-IEc, IGF-IR, IGF-II and IGFBP-2 and IGFBP-3 also increased in expression, while anti-growth factor myostatin mRNA decreased in expression, however these changes did not achieve statistical significance in the RT group. No changes were noted in measures of body composition (i.e. lean mass or fat mass) or circulating CRP, TNF- α or IL-6 following the intervention. Overall, these findings suggest that RT can induce changes in gene expression that may promote protein synthesis and reduce protein degradation in patients with ESRD. Greater adaptation may have been achieved with a larger sample size and/or more potent anabolic intervention.

Physical functioning and quality of life

Physical functioning, including the ability to engage in activities of daily living (Painter, 2005), is lower in patients with CKD as compared to age-matched individuals with normal renal function (Painter, 2005). Deficits in physical functioning have also been documented *via* self-report surveys (DeOreo, 1997; Painter, 2005), performance-based tests (e.g. six-minute walk, gait

speed, strength, sit-to-stand, etc.) (Johansen, Kaysen, et al., 2003; Painter, Carlson, Carey, Paul, & Myll, 2000) and maximal exercise tests (Boyce et al., 1997; Castaneda et al., 2001; Johansen, 1999; Painter, Messer-Rehak, Hanson, Zimmerman, & Glass, 1986). Physical inactivity (Johansen et al., 2000; O'Hare, Tawney, Bacchetti, & Johansen, 2003) and low physical functioning (DeOreo, 1997; Molsted et al., 2007) contribute to reduced quality of life, increased hospitalization, and increased mortality in patients with CKD. Notably, a recent international survey has revealed that physical activity levels are directly proportional to survival in patients with ESRD (Tentori et al., 2010).

Only one study to date has investigated the effect of RT on physical functioning and/or quality of life in pre-dialysis CKD patients. Heiwe *et al.* (Heiwe et al., 2001) prescribed relatively low-intensity (20 repetitions per set) quadriceps muscle training three times per week for 12 weeks in elderly patients with a GFR \leq 25 ml/min and noted significant improvements in isometric quadriceps muscle strength, quadriceps endurance, six minute walk distance, and speed on the 'timed up and go test' from pre to post intervention. However, these functional adaptations were not accompanied by improvements of quality of life.

Several studies have noted improvements in physical functioning and quality of life in patients with ESRD. Cheema *et al.* (Cheema et al., 2007a) noted significant improvements in total body strength ($p < 0.001$), and a trend toward improved six-minute walk distance ($p = 0.16$) secondary to 12 weeks of high-intensity intradialytic RT versus usual care. These improvements in functioning were concomitant with the enhancement of quality of life domains including vitality and physical function (Cheema et al., 2007a). Cheema *et al.* (2007b) have also reported that greater strength adaptation can be achieved with longer durations of intradialytic RT.

Several studies have noted functional adaptations secondary to low-intensity intradialytic RT. Chen *et al.* (2010) found that patients who engaged in approximately six months of lower-body RT experienced significant improvements in knee extensor strength, sit-to-stand movement

time, leisure time physical activity, and self-perceived physical functioning and activities of daily living versus a sham exercise group. Similar functional and/or quality of life adaptations have also been reported in a smaller trials prescribing intradialytic RT (Bullani et al., 2011). By contrast, Orcy *et al.* (2012) did not observe a significant improvement in six-minute walk distance with 10 weeks of isolated, full body RT. However, the RT intervention may have been prescribed at too low an intensity. For example, leg exercises were performed with very light (1-2 lb) ankle cuffs. The exercises prescribed by Chen *et al.* (2010) involved the use of weighted ankle cuffs that could be loaded only up to 20 lbs (9 kg). Johansen *et al.* (2006) also prescribed relatively low-intensity, lower-body exercises and noted significant improvements in the physical function domain of quality of life after 12 weeks of intervention, however, stair climbing, gait speed, or rising from a chair did not significantly improve over time versus the placebo-control condition.

Headley *et al.* (2002) conducted an uncontrolled trial that evaluated the effect of an RT program prescribed during non-dialysis time in 10 patients with ESRD. RT sessions were prescribed twice per week for 12 weeks. During each session, the patients completed 1-2 sets of 10-15 repetitions of nine machine weight exercises (leg press, leg extension, leg curl, chest press, compound row, lateral raise, biceps curl, triceps extension and abdominal curl). Loads were adjusted accordingly with strength adaptation. In addition, the patients were also prescribed an unsupervised home-based RT program that involved the performance of nine exercises (squat, elbow extension, knee flexion, elbow flexion, calf raise, shoulder shrug, hip abduction, scapula retraction and ankle dorsiflexion) using Thera-Band tubing (Akron, OH). The home-based exercises were also prescribed at 1-2 sets of 10-15 repetitions, and heavier resistance bands were utilized in the latter weeks of training. The home-based component of the intervention was delivered *via* a prerecorded video. At the end of the intervention period, the patients significantly

improved peak knee extension isometric strength at 90 degrees of flexion, six-minute walk distance, maximal walking speed, and sit to stand movement time.

Forearm exercise for AV fistula maturation

One of three vascular accesses are typically used to access the blood supply for hemodialysis treatment in patients with ESRD: an arteriovenous (AV) fistula, a synthetic graft, or an intravenous catheter. All vascular accesses must be surgically created. The AV fistula is the preferred vascular access for chronic hemodialysis treatment as it is associated with fewer complications (e.g. thrombosis, stenosis and infection) and a longer functional lifespan versus the synthetic graft (Allon & Robbin, 2002; Churchill et al., 1992; Woods et al., 1997). The preferred site for the creation of an AV fistula or synthetic graft is the forearm (National Kidney Foundation, 2006), and the choice of access is influenced by the condition of the vasculature. The AV fistula and synthetic graft must be given time to heal and mature. In the interim, the patient will receive dialysis *via* an intravenous catheter, the least preferable vascular access for long-term dialysis given that it is most prone to complications.

It is a routine practice to instruct patients to perform arm exercises, especially ball squeezing prior to, and some time after AV fistula surgery, and empirical data support this practice. Robbin *et al.* (2002) determined that patients with an AV fistula adequate for dialysis had a venous diameter >0.4 cm and flow volume >500 ml/min within four months of fistula creation. Recent trials involving forearm resistance exercises have been shown to acutely and chronically increase vessel diameter, cross-sectional area and dilation (Leaf et al., 2003; Oder et al., 2003; Rus et al., 2003).

Oder & Uribarri (Oder et al., 2003) in a trial enrolling 23 hemodialysis patients revealed that five minutes of ball squeezing exercise with the AV fistula-containing arm could acutely

dilate the fistula diameter by about 9.3%. This acute effect may contribute to chronic adaptation of the blood vessels with prolonged training (Leaf et al., 2003; Rus et al., 2003).

Leaf *et al.* (2003) investigated a six-week intervention that combined 10 minutes of pre-exercise forearm heating and RT in five patients with pre-dialysis renal failure. The sessions were prescribed four times per week and exercises involved isometric handgrip contractions at 30-40% of maximal voluntary contractions for 80 to 360s. In addition, the patients repetitively squeezed a squash ball and/or racquet ball. The volume and intensity of isometric exercise was adjusted weekly based on the assessment of grip strength using a handgrip dynamometer and according to patient tolerance. At the end of the training program, the cephalic vein, commonly used to create an AV fistula, significantly increased in cross-sectional area by approximately two fold. The authors concluded that this increase in vessel size and related increase in blood flow might accelerate the maturation of the AV fistula and reduce vascular access-related morbidities.

Rus *et al.* (2003) investigated the effect of handgrip exercise prescribed daily for weeks in 14 hemodialysis patients. The exercises involved the use of a rubber ring (maximum compression force = 50N) and were performed using the non-fistula containing arm. Twenty compressions per minute were performed for a total of 30 minutes. No information regarding training progression was provided. At the end of the intervention period, the participants significantly increased measures of radial artery and average vein diameter. Improvements in brachial artery endothelium-dependent vasodilation were also noted. These effects highlight the importance of handgrip training prior to the construction of the AV fistula as a means to potentially improve fistula maturation.

Hemodialysis-induced catabolism

Hemodialysis treatment, although essential for preserving life in patients with ESRD, also has negative consequences. Recent investigations have shown the hemodialysis treatment itself

can induce skeletal muscle protein catabolism (Raj et al., 2004) marked by increases in pro-inflammatory cytokines (IL-6) and catabolic markers including caspase-3, annexin-V, ubiquitin, and BCKAD-E2 (Raj et al., 2003). Majchrzak *et al.* (2008) recently evaluated the effect of a single session of resistance exercise performed during hemodialysis treatment on protein kinetics in patients with ESRD both during and for 2hr post dialysis treatment. The study employed a randomized crossover design. Eight patients were allocated, in random order, to oral nutritional supplementation (NEPRO®) during dialysis and oral nutritional supplementation (NEPRO®) + resistance exercise during dialysis. The investigators hypothesized that the addition of resistance exercise would lead to augment increases in skeletal muscle protein accretion as compared to nutritional supplementation alone. Three sets of leg press exercise at 75% 1RM were prescribed during the combined (nutrition + resistance) condition. There were no statistically significant differences in protein homeostasis between conditions during dialysis treatment; however, in the post-treatment phase the condition involving resistance exercises resulted in a positive total amino acid balance and a significantly higher forearm muscle net protein balance when compared to nutritional supplementation alone. No differences were noted in whole body protein balance. The researchers concluded that resistance training during dialysis might counteract dialysis-induced protein catabolism.

Notably, however, a follow-up study by the same research group employing a nearly identical intervention over a 6-month period failed to elicit significant increases in lean body mass in patients randomized to oral nutritional supplementation + RT versus those randomized to oral nutritional supplementation only (Dong et al., 2011). The null effect could have been attributed to the fact that only one RT exercise (i.e. leg press) was performed over the entire 6-month intervention. The authors acknowledged the need to test more rigorous RT prescriptions.

The efficacy of intradialytic RT

Painter *et al.* (1986) published the first study to investigate the efficacy of aerobic training (e.g. exercise cycling) prescribed during hemodialysis treatment. This study, and approximately 60 additional reports to date, have clearly demonstrated that exercise training during maintenance hemodialysis treatment is safe, can induce many clinically meaningful and statistically significant health-related adaptations and can result in better compliance than training during non-dialysis time (Konstantinidou, Koukouvou, Kouidi, Deligiannis, & Tourkantonis, 2002; Kouidi, Grekas, Deligiannis, & Tourkantonis, 2004). The findings of studies prescribing intradialytic exercise have been summarized in several recent review articles that provide support for the integration of intradialytic exercise as best practice in ESRD (Cheema, 2008; Cheema, Smith, & Fiatarone Singh, 2005)

Investigations that have prescribed isolated high intensity and low intensity intradialytic RT have reported no life-threatening events, and few adverse events or symptoms (Bullani *et al.*, 2011; Cheema *et al.* 2007a, 2007b, 2011; Chen *et al.*, 2010; Johansen *et al.*, 2006; Kopple *et al.*, 2007; Orcy *et al.*, 2012). Cheema *et al.* (2007a, 2007b) noted that high-intensity intradialytic RT did not exacerbate common dialysis-related complaints including headaches, hypotension, fistula/cannulation difficulties and cramping during a 24-week trial that prescribed intradialytic RT to 49 patients. These findings have been supported by an additional randomized controlled trial (Chen *et al.*, 2010). Adverse events have generally been musculoskeletal (Bullani *et al.*, 2011; Cheema, Lassere, Shnier, & Fiatarone Singh, 2007). For example, Cheema *et al.* (2007a, 2007b) documented only one adverse event induced by the intradialytic RT program, a full-thickness tear of a right supraspinatus muscle in an elderly woman. Investigation suggested that the woman may have been predisposed to this injury (Cheema *et al.*, 2007).

Recruitment data presented in recent randomized controlled trials suggest that the majority of patients in the conventional dialysis setting are medically eligible to engage in RT.

For example, of 278 patients reviewed by Johansen *et al.* (2006), only 60 (22%) were excluded for reasons of illness, medical instability, cognitive impairment, and cancer. Others were excluded due to lower extremity amputation and active drug abuse, however these are not absolute contraindications to exercise, and modifications could be applied to the regimen to accommodate such individuals. Cheema *et al.* (2007a) excluded only 26 of 142 patients (18%) due to a medical contraindication to intradialytic PRT, while Chen *et al.* (Chen et al., 2010) indicated that 66 of 250 patients (26%) did not meet their study eligibility criteria, which were mostly related to unstable chronic disease.

Exercising during hemodialysis is often recommended as a more feasible, convenient, and time-effective solution to promote exercise adherence in ESRD (Cheema, 2008). For example, delivering RT during dialysis may enhance compliance by removing the common cited barriers to exercise participation in this cohort including “lack of motivation,” “lack of time,” and “transportation difficulties (Cheema, 2008). Further, patients are more likely to participate if it is considered normal, “part of the woodwork” and reinforced as beneficial to do so by other patients and the attending health care professionals. While clinically trained exercise physiologists should ideally deliver the program, the endorsement of nephrologists, dialysis nursing staff and renal dietitians is critically important for continued success (Bennett et al., 2010). Unfortunately, many nephrologists and health care professionals appear unaware of the benefits and/or are indifferent to the idea (Johansen, Sakkas, Doyle, Shubert, & Dudley, 2003).

Training packages are now available to establish a cost-effective RT program within any dialysis unit (Iqbal, 2007). As programs become more widely practiced, the demand for novel equipment will be increased and, accordingly, the effectiveness of the interventions will be improved. For example, a novel lower-body RT device customized for the hemodialysis setting has been recently developed by an Australian group (Bennett, Breugelmans, Agius, Simpson-

Gore, & Barnard, 2007). Established, training programs also provide a perfect venue for continued research.

Exercise Recommendations

The research to date suggests that participation in RT is important for patients at high risk of developing CKD and for those diagnosed with CKD and ESRD. RT can play an important role in targeting risk factors including type 2 diabetes, hypertension and obesity and hence can play a key role in reducing the CKD burden that has been forecast for the decades ahead (El Nahas & Bello, 2005). Preliminary data suggest that RT can reduce the decline, or potentially improve renal function (GFR) in patients diagnosed with the CKD, which could potentially contribute to reduced growth of the dialysis population and the reduction of health care expenditures attributed to dialysis care. Moreover RT has been shown to improve many important outcomes in patients with CKD and ESRD, including skeletal muscle wasting, inflammation, physical functioning, and quality of life. Such adaptations may potentially contribute to greater life expectancy in this vulnerable patient population. At present, more robust investigations are required to evaluate the efficacy of RT delivered across the CKD continuum, from at-risk individuals to individuals who have received successful kidney transplants. A broad range of clinically relevant outcome measures should be investigated and greater efforts must be directed toward elucidating the relationship between these adaptations and survival advantage.

There are currently no standardized RT guidelines for individuals with CKD. However, Johansen & Painter (2012) have provided general exercise recommendations that align with the American College of Cardiology and American Heart Association guidelines for exercise testing (Gibbons et al., 2002). We have adapted and added to these recommendations in light of the latest research on RT in patients with CKD and ESRD presented in this chapter:

- Patients with CKD and ESRD are typically older, extremely deconditioned and suffer from a high burden of comorbidities. All patients should undergo appropriate medical screening prior to participating in any structured RT program. It is appropriate to refer patients with known cardiac disease to cardiac rehabilitation programs.
- Exercise programs for patients with CKD should be individually tailored to meet the expectations, goals, needs and preferences of the individual patient. Prescriptions should be holistic and involve aerobic training, RT, balance training and flexibility training elements.
- Evidence suggests that the majority of patients with CKD and ESRD are capable of engaging in and benefitting from low- to high-intensity RT. Training programs can be initiated at low dosages and progressed according to patient tolerance.
- Trainers should be aware of drug-exercise interactions and pay vigilant attention to any untoward symptoms during training. RT sessions should not be undertaken during acute illnesses.
- Intradialytic RT can be safely undertaken by most hemodialysis patients and such programs can be successfully implemented at low cost with the involvement of exercise physiologists and the support of the dialysis nursing staff and nephrologists.
- Intradialytic RT sessions should be initiated within the first two hours of treatment in individuals who commonly experience dialysis-induced symptoms (e.g. hypotension, cramping, headache, nausea, etc.).
- Clinical, health and fitness-related outcomes should be assessed at regular intervals. The findings of such assessments should be shared with the patient and health care providers, including the nephrologist and nursing staff.
- Patients should always be referred to the appropriate allied healthcare professional in cases where the RT prescriber is not qualified to deal with the presenting illness or adverse event

- All patients with CKD should be encouraged to be as physically active as possible. RT should be implemented to complement an active lifestyle. Other forms of exercise should be encouraged (e.g. walking, cycling, yoga, Pilates, group exercise classes, etc.)

Table 1: Stages of Chronic Kidney Disease as defined by the *Kidney Disease Outcome Quality Initiative (K/DOQI)*

Stage	Description	GFR (mL/min/1.73 m ²)	Action
1	Kidney damage with normal or elevated GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, slowing progression, cardiovascular disease risk reduction
2	Kidney damage with mild decrease in GFR	60-89	Estimating rate of progression
3	Moderate decrease in GFR	30-59	Evaluating and treating complications
4	Severe decrease in GFR	15-29	Preparation for kidney replacement therapy
5	Kidney Failure	<15 of dialysis dependent	Kidney transplanted or receiving dialysis

Reference: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis, 39, S1-266, 2002.

Table 2. Resistance training interventions in CKD and ESRD

Subject Characteristics	Resistance Type	Training Prescription	Dependent Variables of Interest	Key Findings in isolated RT group
<p>Castaneda <i>et al.</i> 2001, 2004 Balakrishnan <i>et al.</i>, 2010</p>	<p>Stage 3-4 CKD 14 TRN; 12 P</p>	<p>TRN= knee flexion and extension, lat pull-down, chest and leg press; P=sham movements</p>	<p>3 sets of 8 reps at 80% 1RM, 3x/wk for 12 wks. 1RM tested each month to adjust loading</p>	<p>GFR, muscle CSA, pro-inflammatory cytokines, mtDNA Sig. ↑ in type I, type II CSA, GFR, total body potassium, leucine oxidation, prealbumin, mtDNA, Sig. ↓ in CRP and IL-6.</p>
<p>Heiwe <i>et al.</i> 2001, 2005</p>	<p>Pre-dialysis CKD 16 TRN, 9 CNTL</p>	<p>TRN = knee extensions CNTL= no training</p>	<p>3 sets of 20 reps of knee ext at 60% 1RM, 3x/wk for 12 wks. 1RM tested every 2 weeks to adjust loading</p>	<p>muscle fiber CSA, hematological data, functional measures, QoL No Δ in muscle fiber CSA or QoL, Sig. ↑ in 1RM, muscle endurance, six-min walk, Sig. ↓ in ‘timed up and go’</p>
<p>Headley <i>et al.</i> 2002 Nindl <i>et al.</i> 2004</p>	<p>ESRD 10 TRN</p>	<p>During non-dialysis time; machine weights: leg press, knee extension and flexion, chest press, compound row, lateral raises, biceps curls, triceps extensions and abdominal curls.</p>	<p>1 set of 10-15 reps, 2x weekly at initiation, gradual increase of set/reps every 2-3 weeks. Loads increased with adaptation</p>	<p>isometric strength, functional measures, CRP Sig ↑ in quad isometric strength, six-min walk maximal walking speed Sig. ↓ in CRP, sit to stand time</p>

Cheema <i>et al.</i> 2007a, 2007b 2011	ESRD 24 TRN 19 WLC	Intradialytic RT; free weights: shoulder press, side shoulder raise, triceps extension, bicep curls, external shoulder rotation and bilateral leg raise/leg lift; ankle weights: knee extension, hip flexion and hip abduction; elastic tubing: hamstring curl.	2 sets of 8 reps at RPE 15-17, 3x/wk for 24 weeks. WLC group crossed-over to intervention at week 13	thigh muscle CSA and attenuation, CRP and other cytokines, anthropometrics, functional measures, QoL	Sig. improved muscle attenuation, CRP, anthropometrics, total body strength, physical function and vitality QoL No Δ in IL-1b, IL-6, IL-8, IL-10, IL-12 and TNF- α
Johansen <i>et al.</i> 2006	ESRD 19 TRN+ND, 16 TRN+P, 17 P	Intradialytic RT; ankle weights: knee extension, hip abduction and flexion, ankle dorsiflexion and plantar flexion.	2-3 sets of 10 reps 60% 3RM, 3x/wk for 12 weeks	lean body mass, thigh muscle CSA, strength measures, functional measures, QoL	No Δ in lean body mass Sig. \uparrow in quadriceps CSA, strength measures and physical function QoL. No Δ in gait speed, sit to stand or stair climbing
Chen <i>et al.</i> 2010	ESRD 22 TRN, 22 P	Intradialytic RT; ankle weight: knee extension and flexion, hip adductor and straight leg dorsi/plantar flexion. Seated pelvic tilt without free weight.	2 sets of 8 reps at moderate RPE (6/10) 2x/wk for 48 sessions	functional measures, body composition, QoL and perceived ADL disability	Sig. \downarrow in sit to stand, body fat and ADL disability Sig. \uparrow in knee ext strength, lean body mass, physical functioning QoL

Kopple <i>et al.</i> 2007	ESRD 15 TRN, 15 P	Just prior to dialysis sessions; machine weights: knee extension and flexion, leg press and calf extension.	Wk 1–4: 1 set of 12-15 reps at 70% 5RM; Wk 5–8: 2 sets of 12-15 reps to tolerance; After wk 8: 3 sets of 6-8 reps at 80% 5RM; 3x/wk for 21 weeks	Anabolic and catabolic gene expression, body composition, CRP, TNF- α , IL-6	Sig \uparrow in muscle mRNA IGF-IEa; Non sig \uparrow in other muscle mRNA levels except; Non sig. \downarrow in mRNA myostatin Sig \uparrow in IGF-I protein. No Δ in CRP, TNF- α , IL-6, lean body mass or body fat
Bullani <i>et al.</i> 2011	ESRD 11 TRN	Intradialytic RT; elastic bands with 7 graded resistance: flexion and extension at foot, knee and hip; hip abduction and adduction.	Initial 2-4 wk learning phase, then 3 sets of 20 repetitions at moderate RPE, resistance increased as tolerated, 2x/wk for 4.5 to 6 months	functional measures	Sig \uparrow in Tinetti score (gait and balance); Sig \downarrow in ‘timed up and go’; No Δ in one leg balance or six-min walk
Orcy 2012	ESRD 13 TRN (RT) 13 TRN (RT+AT)	Elastic bands, dumbbells, and ankle weights of 1-2lbs. Elbow flexor, shoulder flexors, hip flexors with knees flexed/extended, hip abductor. Hamstring curl against a therapeutic ball.	3-4 sets of 10-15reps, 3x/wk for 10 wk, progression as tolerated.	Six-minute walk	No Δ in six-min walk
Oder & Uribarri 2003	ESRD 23 TRN	Rubber ball for repetitive squeezing handgrip	Single session, 5 min ball squeezing.	Fistula diameter	Acute sig \uparrow fistula diameter

Leaf <i>et al.</i> 2003	Stage 3-4 CKD 5 TRN	Handgrip dynamometer for isometric handgrip Squash ball and racquet ball for repetitive handgrip	Handgrip dynamometer: 30-40% of MVC for 80–360s, plus repetitive ball squeezing, 4x/wk for 6 months	Cephalic vein size CSA	Sig ↑ in vein CSA with/without tourniquet
Rus <i>et al.</i> 2003	ESRD 14 TRN	Rubber ring (max compression force = 50N) for repetitive handgrip exercise	20 compression/min for 30min, every day for 8 weeks	Radial and brachial arteries blood flow, and diameter Vein diameter	sig ↑ in radial artery and average vein diameter, and brachial artery endothelial function
Majchrzak <i>et al.</i> 2008	ESRD 8 TRN+oral nutrition	Intradialytic RT; patients ambulated to resistance machine for leg press	Single session. 3sets of 12reps at 75%1RM	total amino acid balance, forearm muscle protein balance, whole body protein balance	Positive total amino acid balance post-dialysis (non-sig ↑); Sig ↑ in forearm muscle protein balance; no Δ in whole body protein balance
Dong <i>et al.</i> 2011	ESRD 10 TRN+oral nutrition, 12 oral nutrition	Just prior to dialysis sessions; Pneumatic resistance leg press	3 sets of 12reps at 70%1RM. 1RM re-assessed at month 3 and 6, 3x/wk, 6 months	leg press 1RM, body composition	No Δ in 1RM, percent body fat or lean body mass

TRN= training, P=placebo, CNTL = control, CSA=cross-sectional area, 1RM = one repetition maximum, RPE = rating of perceived exertion, ND = Nandrolone decanoate, IGF = Insulin-like growth factor, IL= Interleukin, MVC = Maximum voluntary contraction, QoL=quality of life, RT = Resistance Training, AT = Aerobic Training

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Appendix 2. Publication – Effect Of Progressive Resistance Training On Measures Of Skeletal Muscle Hypertrophy, Muscular Strength And Health-Related Quality Of Life In Patients With Chronic Kidney Disease: A Systematic Review And Meta-Analysis

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ABSTRACT

Background: Skeletal muscle wasting resulting in reduced muscular strength and health-related quality of life (HRQoL) is common in chronic kidney disease (CKD) and may be reversed with progressive resistance training (PRT). Therefore, we systematically assessed the effect of PRT on measures of skeletal muscle hypertrophy, muscular strength and HRQoL in this cohort to inform clinical practice and guidelines.

Design: Systematic review and meta-analysis.

Inclusion criteria: Randomized controlled trials (RCTs) that investigated the independent effect of PRT (>6 weeks) on measures of skeletal muscle hypertrophy (muscle mass or cross-sectional area [CSA]), muscular strength and/or HRQoL in adults with CKD.

Data extraction and analysis: The standardized mean difference (SMD) from each study was pooled to produce an overall estimate of effect and associated 95% confidence interval (95% CI) between treatment and control groups on primary outcomes.

Results: Seven RCTs in 271 patients with Stage 3-5 CKD yielded seven studies on muscular strength (N=249), six studies on total body muscle mass (N=200), and six studies on HRQoL (N=223). PRT significantly improved standardized muscular strength (SMD = 1.15 [95% CI = 0.80 to 1.49]) and HRQoL (SMD = 0.83 [95% CI = 0.51 to 1.16]), but not total body muscle mass (SMD = 0.29 [95% CI = -0.27 to 0.86]) in our primary analysis. However, secondary analysis of six studies showed that PRT induced significant muscle hypertrophy of the lower extremities (leg mass, or mid-thigh or quadriceps CSA) (SMD = 0.43 [95% CI = 0.11 to 0.76]), a pertinent analysis given that most studies implemented lower body PRT only.

Conclusions: Robust evidence from RCTs indicates that PRT can induce skeletal muscle hypertrophy and increase muscular strength and HRQoL outcomes in men and women with CKD. Therefore, clinical practice guidelines should be updated to inform clinicians on the benefits of PRT in this cohort.

1. INTRODUCTION

According to the *United States Renal Data System*, over 15% of the adult population in the United States (US) has chronic kidney disease (CKD) [1], while global estimates reveal a burgeoning epidemic (8-16% prevalence) [2]. These trends are being driven largely by escalating rates of obesity and type 2 diabetes [3]. The prevention and treatment of CKD will present a major challenge for healthcare systems in the coming decades [3]. A major part of this challenge will involve providing quality care to patients with advanced CKD, including those with pre-dialysis (Stage 3-4 CKD) and end-stage renal disease (ESRD) [3].

Skeletal muscle wasting is common in advanced CKD [4-6] due to factors such as sedentary behavior [7], acidosis [8], co-morbid illnesses, corticosteroid usage, aging, oxidative stress, dialysis treatment [9], insulin resistance, chronic inflammation and protein-restricted diet. This wasting contributes to reductions in muscular strength and associated functional impairment [10-12]. Functional impairment, in turn, contributes to impaired health-related quality of life (HRQoL), particularly the physical dimension of HRQoL [13]. Many investigations have shown that muscle wasting [14], loss of functional activities [15] and/or low HRQoL contribute to greater hospitalization and all-cause mortality in patients with CKD [16-18].

Progressive resistance training (PRT) has been shown to induce skeletal muscle hypertrophy and improve functioning and HRQoL in older adults and those with advanced chronic diseases [19]. Since there is an association of muscle wasting in CKD with high morbidity and mortality, it has been hypothesized that PRT may be important in terms of clinical outcomes in this patient population as well [20-24]. In fact, Exercise and Sport Science Australia has recently recommended PRT as a central component of the exercise prescription for patients with CKD [25]. Since 2001, a number of randomized controlled trials (RCTs) have investigated the independent effect of PRT on measures of skeletal muscle hypertrophy and related health

outcomes in patients with CKD [26-32]. However, there is currently no consensus regarding the effectiveness of PRT for counteracting catabolic disease outcomes in this cohort [25]. Accordingly, PRT is not routinely prescribed [33] and recommendations for undertaking this form of exercise remain absent from CKD clinical practice guidelines [34].

Our initial analysis of the published literature indicated an absence of high quality reviews specifically elucidating the effect of PRT in patients with CKD. We therefore conducted a systematic review of the literature to assess the independent effect of PRT on measures of skeletal muscle hypertrophy, muscular strength and HRQoL in patients with CKD to inform clinical practice and guidelines.

2. METHODS

2.1 Search strategy

A systematic review of all published literature using the following electronic databases was conducted in June 2013: MEDLINE (OvidSP, Wolters Kluwer), PubMed (NCBI, U.S. National Library of Medicine), ScienceDirect (SciVerse, Elsevier), SPORTDiscus (EBSCOhost, EBSCO), Scopus (SciVerse, Elsevier), Web of Science (Web of Knowledge, Thomson Reuters), the Cochrane Library (John Wiley & Sons), Embase (OvidSP, Wolters Kluwer), CINAHL, and Google Scholar. Search syntaxes were developed in consultation with an experienced university librarian taking into account a broad range of terms and phrases used in definitions related to CKD (e.g. chronic kidney disease, hemodialysis, end-stage renal disease, etc.) and resistance training (e.g. resistance training, resistance exercise, weight training, weight lifting, strength training, etc.). Sample search strategies (PubMed and Scopus) have been presented in Electronic Supplementary Material, Appendix S1. Reference lists of retrieved full-text articles and recent reviews were examined to identify additional articles not found by our search.

2.2 Study selection

Electronic references were compiled in an Endnote X6© (Thomson Reuters) file and duplicates were identified and deleted. Two authors (BSC and DC) independently reviewed the titles and abstracts of each reference for potential inclusion. Each reviewer then performed a second screening on the full text version of these articles, and disagreements were resolved by discussion. RCTs that investigated the independent effect of PRT intervention on measures of skeletal muscle hypertrophy (muscle mass or cross-sectional area [CSA]), muscular strength and/or HRQoL in adults with CKD (Stage 1 to 5) were eligible. PRT interventions may have included, but were not restricted to, any form of resistive type exercise using body weight (calisthenics), equipment (machine weights, free weights) or apparatus (elastic bands), and had to have been at least six weeks in duration. There were no language restrictions for articles.

2.3 Primary outcomes

The primary outcomes were the mean difference in measures of skeletal muscle hypertrophy (muscle mass or CSA), muscular strength and HRQoL after intervention (post-treatment) between the treatment and control (e.g. non-treatment, placebo-treatment) group. Where multiple muscular strength outcomes were reported, we prioritized lower body over upper body measures, and knee extension over other lower body measures. Where multiple measures of muscle mass or CSA were reported, we prioritized measures of muscle mass over CSA, and whole body over regional measures. Where multiple HRQoL outcomes were reported, first we prioritized subscales then summary measures of the physical component of HRQoL.

2.4 Data extraction

Data extraction and quality assessment of included studies were performed and/or verified independently by three reviewers (BSC, DC and PF). Discrepancies were resolved through discussion. Authors of relevant studies were contacted, where possible, for data that could not be extracted from the published articles.

2.5 Quality assessment

The following data were extracted from included studies using a standard proforma: study design, study population characteristics, PRT intervention (e.g. specific exercises, number of sets per exercise, number of repetitions per set, intensity (load), frequency and duration of training and loading progression). Our quality checklist was designed based on established criteria for the assessment of RCTs [35]. Quality items for RCT studies reviewed were (each worth 1.0 numerical point) as follows: (1) evidence of randomization and concealment of treatment allocation, (2) statistical similarity of groups at baseline, (3) specification of eligibility criteria, (4) blinding of outcomes assessors, (5) reporting of compliance, (6) supervision of exercise sessions, (7) reporting of dropouts, (8) presenting data for primary and secondary outcomes, (9) use of intention-to-treat analysis, and (10) reporting of adverse events. Summed scores to range from 0 to 10 points with higher scores reflecting better quality. Data extraction and quality assessment were completed and checked by two reviewers (BSC and DC).

2.6 Data synthesis

Three reviewers (DC, BSC and EA) independently collated and/or verified extracted data to present a descriptive synthesis of important study characteristics and a quantitative synthesis of effect estimates.

2.7 Secondary outcomes

The secondary outcomes were data about adverse events for a descriptive synthesis.

2.8 Statistical methods

We pooled and weighted studies first using random effects meta-analysis models, and second using fixed effects models for verification [36]. The effect was measured as the difference between groups in the improvement in outcome over the treatment period. Where papers did not present the mean and standard deviation of the improvement in outcome, we estimated these from the pre- and post-treatment standard deviations [37]. This estimation requires an estimate of the pre- post correlation which we obtained from papers which provided pre-, post- and change means and standard deviations [37]. As the estimated correlations were quite consistent across studies (Electronic Supplementary Material, Table S1) we used the average correlation in our calculations.

In examining the effects of PRT on skeletal muscle hypertrophy, muscular strength and HRQoL outcomes, the standardized mean difference (SMD) from each study was pooled to produce an overall estimate of effect and associated 95% confidence interval (95% CI) between treatment and control groups. For each meta-analysis model, the degree of heterogeneity in SMDs was assessed by visual inspection, the I^2 statistic (moderate being < 50%) [38] and the χ^2 -test of goodness of fit [39]. Where evidence of heterogeneity was observed, we checked data extracted from individual outlier studies, qualitatively investigated reasons for their different results, and explored the effects of study exclusion in sensitivity analyses.

The subset of studies examining the impact of PRT on lean body mass (in kilograms) as measured by dual-energy X-ray absorptiometry (DEXA) were pooled to estimate the inverse variance weighted mean difference (WMD), including the DerSimonian and Laird 95% CI, between cases and controls. This preserved the original measurement units. We also used

sensitivity analysis to investigate the robustness of the meta-analyses models. We variously excluded studies that combined PRT with other therapies (including hemodialysis), studies in older patients (> 60 years), studies conducted outside the US, longer duration trials (≥ 12 weeks), and studies of lower quality (score < 6.0). Publication bias, which reflects the tendency for smaller studies to be published in the literature only when findings are positive, was assessed visually using funnel plots [40]. All calculations were performed in Stata version 12 (StataCorp, College Station, TX, USA) using the 'metan' and 'metafunnel' commands. A two-tailed P -value < 0.05 was considered statistically significant throughout the analyses.

3. RESULTS

Figure 6.1 presents a flowchart summarising identification of potentially relevant studies, and those included. Our search strategy identified 187 citations after duplicates were removed. Of these, 164 citations were excluded after the first screening of titles and/or abstracts for inclusion and exclusion criteria. After further assessment of the remaining 23 citations, 16 were excluded (Electronic Supplementary Material, Appendix S2) for reasons listed in Figure 6.1, leaving 7 for inclusion in the review. Most citations were excluded due to no randomization or due to being redundant citations of the same study.

3.1 Descriptive data synthesis

Table 1 presents study characteristics of the seven RCTs included for review, which were published between 2001 and 2013. Four of seven studies were conducted in the US [26, 28, 30, 31] with others conducted in Australia [27], Brazil [29], and South Korea [32]. The major inclusion criterion was pre-dialysis (Stage 3-4) CKD [30] or ESRD [26-29, 31, 32]. All studies in ESRD involved maintenance hemodialysis patients. In most of these studies it was noted that

the patients were adequately dialyzed ($Kt/V > 1.2$) and receiving dialysis treatment for more than 3 months. Major exclusion criteria primarily emphasized uncontrolled cardiovascular diseases and other conditions that would contraindicate PRT. Analysed sample sizes ranged from 22 to 68, resulting in a total of 271 participants across studies. Mean age of the samples ranged from 43 to 69 years. All studies enrolled both men and women. PRT interventions were prescribed two to three times per week during hemodialysis treatment in four studies with all employing weighted ankle cuffs [26-29]. Only three studies targeted both the upper and lower body musculature with PRT exercises [27, 30, 32], while four targeted the lower body musculature only [26, 28, 29, 31]. Two studies prescribed PRT just prior to each hemodialysis treatment session (3 sessions/wk) using machine weights [31] or elastic bands and sandbags [32]. Only one study was conducted in patients not receiving hemodialysis and prescribed PRT using standard machine weights three sessions per week [30]. Three studies compared PRT intervention to usual care (no exercise) [27, 29, 32], one study compared PRT to stretching exercise using light resistance bands [28], one study compared PRT plus nutritional supplementation with nutritional supplementation only [31] and one study compared PRT plus a protein restricted diet to protein-restricted diet only. Further, a study by Johansen *et al.* [26] compared PRT + anabolic steroid (i.e. nandrolone decanoate) to anabolic steroid only and PRT + placebo to placebo only. Hence, this study was included as two separate comparisons in relevant meta-analyses. Trial durations ranged from 8 to 24 weeks.

Primary outcomes were muscular strength measures evaluated by knee extension [26-28, 30] and leg press [31, 32], total body muscle mass measures evaluated by total body potassium [30], DEXA [26, 28, 31] and bioelectrical impedance analysis (BIA) [32], mid-thigh muscle CSA evaluated by computed tomography (CT) [27, 30], quadriceps muscle CSA evaluated by magnetic resonance imaging (MRI) [26], lean leg mass evaluated by DEXA [28, 31], and the physical dimension of HRQoL evaluated by the Medical Outcomes Trust Short Form-36 (SF-36) physical functioning domain [26, 27, 29] and physical component summary scale [28, 32]. Mean

quality scores ranged from 5.5 to 9.5, and five studies received a score of 8.0 or higher (Electronic Supplementary Material, Table S2).

3.2 Quantitative data synthesis

Figure 2 presents the SMD for muscular strength outcomes after PRT between the treatment and control groups. PRT significantly improved standardized muscular strength outcomes compared with control conditions (SMD = 1.15 [0.80, 1.49]), and there was only slight evidence of statistical heterogeneity between studies ($I^2=35.0%$, $P=0.161$). The sensitivity analyses presented in Table 2 shows that the pooled SMD was similarly large in the fixed effect model after each of the various studies was excluded (SMD = 0.82 to 1.36). In addition, a funnel plot was produced and showed little evidence of publication bias, since the SMD in muscular strength outcomes was consistently medium to large in all studies (Electronic Supplementary Material, Figure S1).

Figure 3 presents the SMD for total body muscle mass outcomes after PRT between the treatment and control groups. Our primary analysis revealed that PRT failed to increase standardized total body muscle mass outcomes compared with control conditions (SMD = 0.29 [-0.27, 0.86]; $I^2=73.5%$, $P=0.002$). A funnel plot showed no evidence of publication bias (Electronic Supplementary Material, Figure S2). The sensitivity analyses showed that this null effect was comparable after each of the various studies was excluded (Electronic Supplementary Material, Table S3). Conversely, PRT significantly improved total body muscle mass in the fixed effect model (SMD = 0.34 [0.05, 0.63]) but the fixed effect assumption was violated given the strong evidence of statistical heterogeneity between studies ($I^2=73.5%$, $P=0.002$).

Given that the majority of trials reviewed investigated the effect of lower body PRT only (Table 1), we pooled studies to investigate the SMD in lower body muscle mass and CSA outcomes in a secondary analysis (Figure 4). This analysis of six studies showed that PRT

induced significant muscle hypertrophy of the lower extremities (leg mass, or mid-thigh or quadriceps CSA) (SMD = 0.43 [0.11, 0.76]; $I^2 = 26.8\%$, $P = 0.234$). A funnel plot showed little evidence of publication bias (Electronic Supplementary Material, Figure S3). Additionally, we pooled studies to estimate the inverse variance weighted mean difference (WMD) in muscle mass outcomes after PRT between the treatment and control groups. PRT significantly improved quadriceps muscle CSA measured by MRI (pooled WMD for two studies [26] was 3.83 cm² [1.73, 5.94]; $I^2 = 1.0\%$, $P = 0.315$), but not total body muscle mass measured by DEXA only (pooled WMD for four studies [26, 28, 31] was -0.06 kg [-1.94, 1.83]) or thigh muscle CSA measured by CT (pooled WMD for two studies [27, 30] was 3.03 cm² [-0.15, 6.21]).

Figure 5 presents the SMD for HRQoL outcomes after PRT between the treatment and control groups. PRT significantly improved standardized HRQoL outcomes compared with control conditions (SMD = 0.83 [0.51, 1.16]), and there was little evidence of statistical heterogeneity between studies ($I^2 = 27.8\%$, $P = 0.226$). The sensitivity analyses presented in Table 3 shows that the pooled SMD was similarly large in the fixed effect model and after each of the various studies was excluded (SMD = 0.70 to 0.94). In addition, a funnel plot was produced and showed little evidence of publication bias, since the SMD in HRQoL outcomes was consistently medium to large in all studies (Electronic Supplementary Material, Figure S4).

3.3 Adverse events

Four studies reported that no adverse events occurred as a consequence of PRT [27, 28, 30, 32]. One study that prescribed intradialytic PRT reported no statistically significant differences between the experimental and control group in the number of dialysis-related complaints (i.e. headache, hypotension, cramping, and fistula cannulation difficulties), falls, acute illnesses, and number of visits to health care professionals [27]. However, one adverse event was documented in this study: A 73-year-old woman in the PRT group sustained a partial

tear of the right supraspinatus. The injury was documented [41] and managed conservatively; the patient resumed lower body PRT for the remainder of the trial [27]. One study reported on adverse events related to anabolic steroid use, but not in relation to PRT [26]. Two studies did not report on adverse events [29, 31].

4. DISCUSSION

4.1 Summary of the evidence

Based on RCT evidence in patients with CKD, our results were consistent and indicate that PRT significantly improves measures of muscular strength (SMD = 1.15 [0.80, 1.49]) and HRQoL (SMD = 0.83 [0.51, 1.16]). There was an absence of evidence showing that PRT significantly increases total body muscle mass (SMD = 0.29 [-0.27, 0.86]). However, secondary analysis of lower body muscle mass and CSA outcomes (i.e. leg mass, or mid-thigh or quadriceps CSA) revealed a significant effect for PRT versus control conditions (SMD = 0.43 [0.11, 0.76]), a pertinent analysis given that the majority of trials (4/7) were limited to lower body training [26, 28, 29, 31]. Overall, this robust evidence from RCTs indicates that PRT can induce skeletal muscle hypertrophy and increase muscular strength and HRQoL with no risk of serious adverse events in men and women with CKD.

The size of the effect of PRT on these key outcomes is moderate to large, and clinically relevant. For instance, studies have consistently shown that skeletal muscle wasting is a strong predictor of mortality in patients with ESRD [14, 42, 43], and a recent observational study noted that the loss of muscle is particularly rapid in pre-dialysis CKD [10]. Carrero *et al.* [43] have shown that incident and prevalent hemodialysis patients (dialysis vintage = 8 to 78 months) with mild to moderate/severe muscle wasting (SMD = 0.38 to 0.69) suffer a greater risk of systemic inflammation (odds ratio = 2.81 [1.33, 5.91]), cardiovascular disease (odds ratio = 3.08 [1.43,

6.65]) and all-cause mortality (hazard ratio = 1.29 to 3.04) compared to CKD patients with no evidence of muscle wasting. Similarly, studies have shown that the loss of muscular strength (SMD = 0.66) is associated with significantly greater risk of renal endpoint (i.e. pre-dialysis mortality or reaching ESRD) in CKD [44] while impairments in the physical component of HRQoL (SMD = 0.60) have been shown to predict mortality [45]. Therefore, the results of our study suggest that the size of the effect of PRT on skeletal muscle hypertrophy (SMD = 0.43 [0.11, 0.76]), muscular strength (SMD = 1.15 [0.80, 1.49]) and HRQoL (SMD = 0.83 [0.51, 1.16]), which could be expected in practice, could theoretically protect against disease-related complications and reduce the mortality burden in patients with CKD. Hence, our findings are clinically relevant.

Notably, the effect of PRT on muscle strength and HRQoL outcomes remained robust in fixed effect models and after exclusion of studies that combined PRT with other therapies (including hemodialysis), studies in older patients, studies conducted outside the US, longer duration trials, and studies of lower quality. In summary, our results indicate that PRT should be considered for inducing muscle hypertrophy and increasing muscular strength and HRQoL outcomes in men and women with CKD.

4.2 Limitations

Several limitations require careful consideration. Since only a small number of studies were included, the findings of this review may not be relevant to other countries and key groups within the CKD population. In particular, most of the RCTs reviewed were conducted in patients with ESRD undergoing hemodialysis treatment, while only one trial enrolled patients with pre-dialysis CKD. We found no RCTs that tested the efficacy of PRT in patients undergoing peritoneal dialysis or kidney transplant and hence research on these unique CKD populations is required. Second, there was heterogeneity with respect to the exercise prescriptions (Table 1).

Several studies did not prescribe full body PRT, while others prescribed low-intensity [26, 29] or few exercises [26, 29, 31], factors that can potentially reduce the effectiveness of PRT. It has been shown that patients with CKD can safely tolerate higher intensity and more comprehensive PRT regimens (i.e. involving a greater number of exercises) [27, 30]. Such programs, involving longer training durations, are likely to be most effective in terms of adapting outcome measures. However, we did not investigate any dose-response effects in the present review and accordingly, the optimal dosages of PRT to adapt the specific outcomes in this cohort remain unknown and require further research. Finally, combined across all studies, the total number of participants is relatively modest (n = 200 to 249).

5. CONCLUSIONS

We believe that our meta-analytic results are sufficiently reliable to recommend that clinicians consider prescribing PRT for inducing skeletal muscle hypertrophy and increasing muscular strength and HRQoL outcomes in patients with CKD. Future high quality research is needed to clarify the long-term clinical benefits and risks of PRT in this cohort.

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Table 1: Characteristics of randomized controlled trials reviewed

Reference	Sample (n)	Population	Mean age (y)	Treatments	Control conditions	Trial duration (wk)	Outcomes (assessments; units)	Quality score (/10)	
		Inclusion criteria		Exclusion criteria					
Castaneda <i>et al</i> , 2001 USA	26	Serum creatinine 1.5-5.0 mmol/l; physician approval to follow low-protein diet; confirmed CKD diagnosis by nephrologist (<i>via</i> renal biopsy and clinical records)	65	Myocardial infarction within previous 6 mo.; any unstable chronic condition, dementia, alcoholism, dialysis or previous renal transplant; current resistance training; recent involuntary weight change; albumin <30 g/l, proteinuria >10 g/l; abnormal exercise stress test results	Standard PRT using machine weights (knee extension, knee flexion, lat pull down, chest press, leg press) 3 sets x 8 reps at 80% 1RM, 3 sessions/wk, 1RM tested each month to adjust loading, plus protein-restricted diet (0.6 g/kg per day)	protein-restricted diet (0.6 g/kg per day)	12	Muscle (total body potassium (kg), mid-thigh muscle CSA via CT (cm ²), type I and II muscle fibre CSA (µm ²)); dynamic 1RM upper body strength (chest press, lat pulldown; kg), dynamic 1RM lower body strength (leg press, knee extension, knee flexion; kg)	8.5
Johansen <i>et al</i> , 2006 USA	68	Adequate dialysis (Kt/V≥1.2) and compliant with hemodialysis treatment (i.e. missing <2 treatment sessions over previous month)	56	Hemodialysis <3 mo.; catabolic state (e.g. HIV with opportunistic infection, malignancy, or infection requiring intravenous antibiotics over prior 2 mo.; unable to provide informed consent; active intravenous drug use; thigh graft; contraindications to PRT	(a) PRT during dialysis using weighted ankle cuffs (knee extension, hip abduction and flexion, ankle dorsiflexion and plantarflexion), 2–3 sets x 10 reps at 60% 3RM, 3 sessions/wk, weights increased when patient could perform 3 sets x 10 reps, plus placebo injection weekly (b) Intervention a + nandrolone decanoate injection weekly (men=200 mg/dose; women=100mg/dose)	(a) placebo injection weekly (b) nandrolone decanoate injection administered weekly (men=200 mg/dose; women=100mg/dose)	12	Muscle (lean body mass via DEXA (kg), quadriceps muscle CSA via MRI (cm ²), serum creatinine (mg/dl)); dynamic lower body strength (knee extension, hip abduction, hip flexion; lb.); isokinetic lower body strength (knee extension at 90 and 120 deg/s; Nm); HRQoL (SF-36 physical function)	8

Cheema <i>et al</i> , 2007	49	Adult (≥ 18 yr); hemodialysis >3 mo.; independent ambulation with or without assistive device; adequately dialyzed ($Kt/V \geq 1.2$); stable during dialysis; ability to provide written informed consent; willingness to be randomly assigned and undergo protocols	Acute or chronic medical conditions that would preclude PRT or collection of outcome measures	63	PRT during dialysis using weighted dumbbells (shoulder press, side shoulder raise, triceps extension, biceps curl, external rotation), weighted ankle cuffs (seated knee extension, supine hip flexion, supine hip abduction, supine straight-legged raise), elastic tubing (seated hamstring curl) and body weight (bilateral leg raises - seated or supine), 2 sets x 10 reps at RPE 15-17, 3 sessions/wk	usual care (no exercise)	12	Muscle (mid-thigh muscle CSA via CT; cm^2); total body isometric muscular strength (knee extensor + hip abductor + tricep, kg); isometric knee extensor strength ^a (kg); HRQoL (SF-36 physical function)	9.5
Australia									
Chen <i>et al</i> , 2010	44	Age ≥ 30 yr; serum albumin <4.2 g/dl and hemodialysis thrice weekly for >3 mo. with $\geq 80\%$ compliance	Unstable cardiovascular disease; any uncontrolled chronic condition; cardiac surgery, retina laser therapy, myocardial infarction, joint replacement or lower extremity fracture in previous 6 mo.; severe cognitive impairment; lower extremity amputation; current strength training	69	PRT during first 2hr of hemodialysis using weighted ankle cuffs (knee extension, dorsi/plantar flexion, leg curl, inner leg raises, dorsi/plantar flexion with straight legs, seated pelvic tilt) first 8 sessions with no loading (RPE 2-4/10) progressed to 1-2 sets x 8 reps (RPE 6/10), 2 sessions/wk	Stretching exercises using light resistance bands, 2 sets, 20-30s/stretch	18	Muscle (lean whole-body mass and lean leg mass via DEXA (kg); muscle strength (knee extensor; kg), HRQoL (SF-36 physical and mental component summary scales)	8
USA									
Dong <i>et al</i> , 2011	22	Age >18 yr; thrice weekly hemodialysis for >3 mo.; adequate dialysis ($Kt/V >1.2$), using a biocompatible dialysis membrane	Active inflammatory or infectious disease; pregnancy, hospitalization within previous 1 mo.; with cardiovascular disease and/or osteoarthritis and unable to exercise	43	PRT prior to each hemodialysis treatment using pneumatic resistance equipment (leg press only), 3 sets x 12 reps at 70% 1RM. 1RM tested at month 3 for load adjustment, plus same nutritional supplement as control, 3 sessions/wk	Nutritional supplement: 2 cans of lactose-free formula (Nephro®) containing 240mL and 480 kcal (66.8 kcal from protein, 211.2 kcal from carbohydrates and 204.3 kcal from fat), taken 3	24	Muscle (lean body and leg mass via DEXA (kg, %); muscle strength (leg press 1RM; lb.)	6.5
USA									

						times/wk during dialysis			
Song <i>et al</i> , 2012	40	Age >18 yr; hemodialysis for >3mo.; permission of nephrologist; ability to maintain a seated position; independent ambulation with or without an assistive device; adequate dialysis (Kt/V=1.2); stable during dialysis; willingness to be randomly assigned and undergo study protocols	None specified.	53	PRT prior to each hemodialysis treatment using elastic bands (6 upper body exercises) and sandbags (6 lower body exercises), 3 sets x 10-15 reps at RPE 11-15, 3 sessions/wk.	usual care (no exercise)	12	Muscle (lean body mass via BIA; kg); muscle strength (grip and leg strength; kg); HRQoL (SF-36 physical and mental component summary scales)	8
South Korea									
de Lima <i>et al</i> , 2013	22	Age 18-75 yr; thrice weekly hemodialysis; men and women; sedentary	Uncontrolled arterial hypertension; ischemic cardiopathy; amputation; deep vein thrombosis; excessive pallor; severe dyspnea; femoral fistula; arrhythmias; precordial pain; orthopedic or neurological condition and cognitive alterations affecting participation	47	PRT during first 2hr of dialysis using weighted ankle cuff (knee flexion/knee extension, and hip and knee flexion with foot dorsiflexion), 3 sets x15 reps at 40% 1RM, 3 sessions/wk. 1RM tested every 15 days for load adjustment.	usual care (no exercise)	8	HRQoL ^a (SF-36 physical functioning)	5.5
Brazil									

Abbreviations: USA=United States of America; CKD=chronic kidney disease; HIV= human immunodeficiency virus; Kt/V=hemodialysis treatment adequacy; CT=computed tomography; DEXA=dual energy X-ray absorptiometry; MRI=magnetic resonance imaging; BIA=bioelectrical impedance analysis; PRT=progressive resistance training; RM=repetition maximum; lat=latissimus dorsi; reps=repetitions; HRQoL=health-related quality of life; SF-36=Medical Outcomes Short-Form 36 Quality of Life Questionnaire; CSA=cross-sectional area; ^aData requested and received from authors (not available in publication)

Table 2: Sensitivity analysis of randomized controlled trials investigating muscular strength outcomes

Sensitivity analysis	Studies (n)	Sample (n)	SMD	LCL	UCL	P-value	I^2	P-value
Fixed effects model	7	249	1.13	0.86	1.4	<0.001	35	0.161
Exclusion of 1 study involving PRT + nandrolone decanoate	6	217	1.1	0.72	1.49	<0.001	41.8	0.126
Exclusion of 3 studies in cohorts >60 yr	4	130	1.06	0.62	1.49	<0.001	24.7	0.263
Exclusion of 2 studies outside USA	5	160	1.36	0.98	1.74	<0.001	15.3	0.317
Exclusion of 1 study in non-dialysis CKD	6	223	1.15	0.75	1.54	<0.001	45.8	0.1
Exclusion of 2 studies on PRT + diet	5	201	1.22	0.79	1.66	<0.001	49.7	0.093
Exclusion of 2 studies of longer duration	5	183	1.05	0.74	1.37	<0.001	0	0.426
Exclusion of 4 studies prescribing PRT during dialysis time	3	110	0.82	0.38	1.26	<0.001	0	0.633

SMD=standardized mean difference, LCL=lower confidence interval, UCL=upper confidence interval, I^2 =I-squared statistic, PRT=progressive resistance training and

CKD=chronic kidney disease

Table 3: Sensitivity analysis of randomized controlled trials investigating health-related quality of life outcomes

Sensitivity analysis	Studies (n)	Sample (n)	SMD	LCL	UCL	P-value	I^2	P-value
Fixed effects model	6	223	0.83	0.56	1.11	<0.001	27.8	0.226
Exclusion of 1 lower quality study (score <6.0)	5	201	0.85	0.46	1.23	<0.001	41.9	0.142
Exclusion of 2 studies in cohorts >60 yr	4	130	0.73	0.38	1.09	<0.001	0	0.474
Exclusion of 1 study involving PRT + nandrolone decanoate	5	191	0.94	0.63	1.24	<0.001	1.2	0.399
Exclusion of 3 studies outside USA	3	112	0.87	0.19	1.56	0.012	66.3	0.052
Exclusion of 1 study of longer duration	5	179	0.7	0.4	1	<0.001	0	0.622

SMD=standardized mean difference, LCL=lower confidence interval, UCL=upper confidence interval; I^2 =I-squared statistic, PRT=progressive resistance training and CKD=chronic kidney disease

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Electronic Supplementary Material

Electronic Supplementary Material, Appendix S1. PubMed and Scopus search syntax

"kidney diseases"[MeSH Terms] OR kidney disease[Text Word] OR renal disease[Text Word]
OR "renal insufficiency, chronic"[MeSH Terms] OR "kidney failure, chronic"[MeSH Terms] OR
Chronic Renal Insufficiency[Text Word] OR End Stage Renal Disease[Text Word] OR chronic
renal disease[Text Word] OR end-stage renal failure[Text Word] OR "renal dialysis"[MeSH
Terms] OR renal dialysis[Text Word] OR "dialysis"[MeSH Terms] OR hemodialysis[Text Word]
OR haemodialysis[Text Word] AND "resistance training"[MeSH Terms] OR Resistance
Training[Text Word] OR Strength Training[Text Word] OR Resistance exercise [Text Word] OR
"weight lifting"[MeSH Terms] OR weight training [Text Word] OR Weight-lifting[Text Word]
OR "weight-bearing"[MeSH Terms] OR weight bearing[Text Word] OR Weight-bearing [Text
Word] OR Resistance exercise program*[text Word]

(TITLE-ABS-KEY("Resistance Training" OR "Strength Training" OR "Resistance exercise" OR
"weight lifting" OR "weight training" OR "weight bearing" OR "Resistance exercise program*"))
AND ((TITLE-ABS-KEY("kidney disease" OR "renal disease" OR "renal insufficiency" OR
"kidney failure" OR "chronic renal insufficiency" OR "end stage renal disease" OR "end stage
renal failure" OR "end stage kidney disease" OR "chronic kidney disease") OR TITLE-ABS-
KEY("renal dialysis" OR "renal Failure" OR *modialysis OR dialysis OR CKD))

Electronic Supplementary Material, Table S1

Outcome	Paper	Computed correlation	
		Treatment group	Control group
Change in muscle mass	Castaneda et al, 2001 ^[30]	0.95	0.91
	Johansen et al, 2006a ^[26]	0.97	0.94
	Johansen et al, 2006b ^[26]	0.99	0.97
	Song et al, 2012 ^[32]	0.96	0.98
Change in knee extension strength	Johansen et al, 2006a ^[26]	0.81	0.70
	Johansen et al, 2006b ^[26]	0.74	0.63
	Song et al, 2012 ^[32]	0.89	0.91
Change in health-related quality of life (HRQoL)	Johansen et al, 2006a ^[26]	0.87	0.78
	Johansen et al, 2006b ^[26]	0.94	0.96
	Cheema et al, 2007 ^[27]	0.90	0.89
	Song et al, 2012 ^[32]	0.66	0.68

Electronic Supplementary Material, Appendix S2. Excluded citations

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14. Nindl BC, Headley SA, Tuckow AP, Pandorf CE, Diamandi A, Khosravi MJ, Welles R, Jones M, Germain M: IGF-I system responses during 12 weeks of resistance training in end-stage renal disease patients. *Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society* 2004, 14(3):245-250.
15. Segura-Ortí E, Kouidi E, Lisón JF: Effect of resistance exercise during hemodialysis on physical function and quality of life: Randomized controlled trial. *Clinical Nephrology* 2009, 71(5):527-537.
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Electronic Supplementary Material, Table S2. Quality items checklist for randomized controlled trials

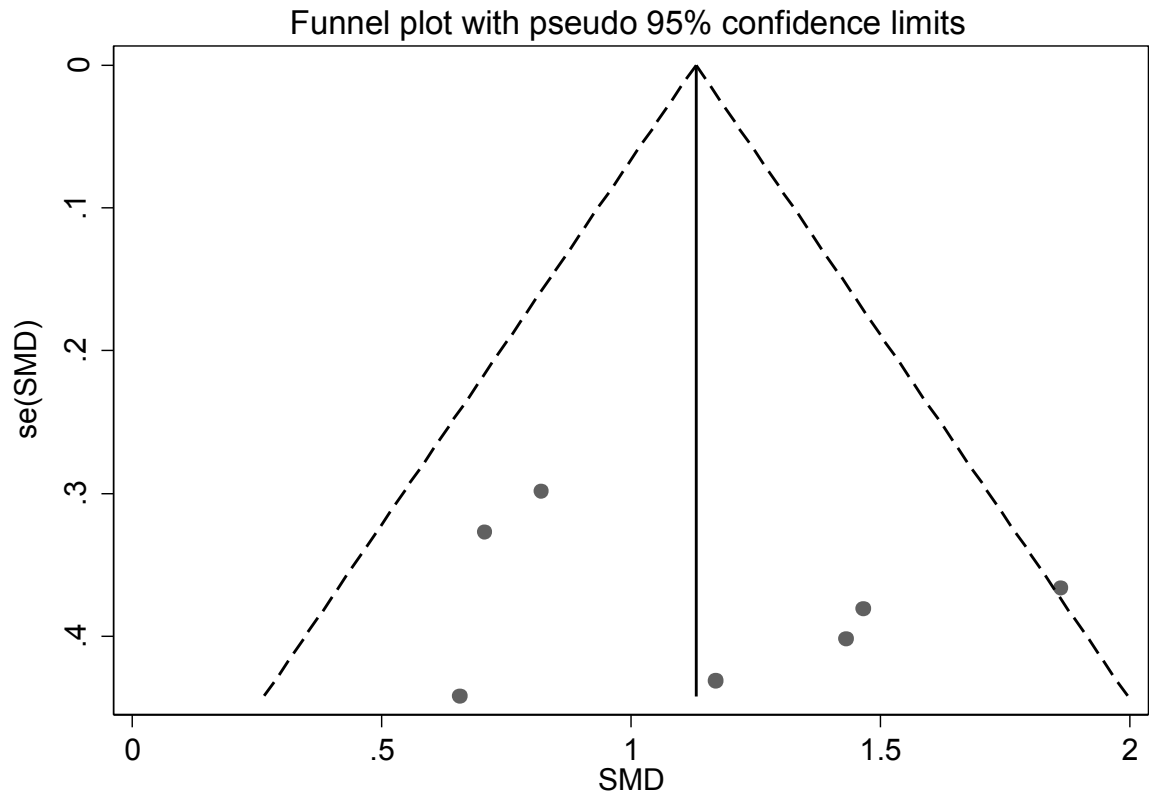
Study identification	Treatment Allocation (each worth 0.5 points): (1) evidence of randomization method; (2) evidence of concealment of treatment allocation	Were groups similar at baseline regarding the most important prognostic indicators?	Were the eligibility criteria specified?	Were outcomes assessors blinded?	Was compliance to the intervention reported?
Castaneda <i>et al</i> , 2001	0.5	1.0	1.0	0.5	1.0
Johansen <i>et al</i> , 2006	1.0	1.0	1.0	0.0	1.0
Cheema <i>et al</i> , 2007	1.0	1.0	1.0	0.5	1.0
Chen <i>et al</i> , 2010	1.0	1.0	1.0	0.0	1.0
Dong <i>et al</i> , 2011	0.5	1.0	1.0	0.0	1.0
Song <i>et al</i> , 2012	0.5	1.0	1.0	0.5	1.0
de Lima <i>et al</i> , 2013	1.0	1.0	1.0	0.0	0.0

(continued >>>)

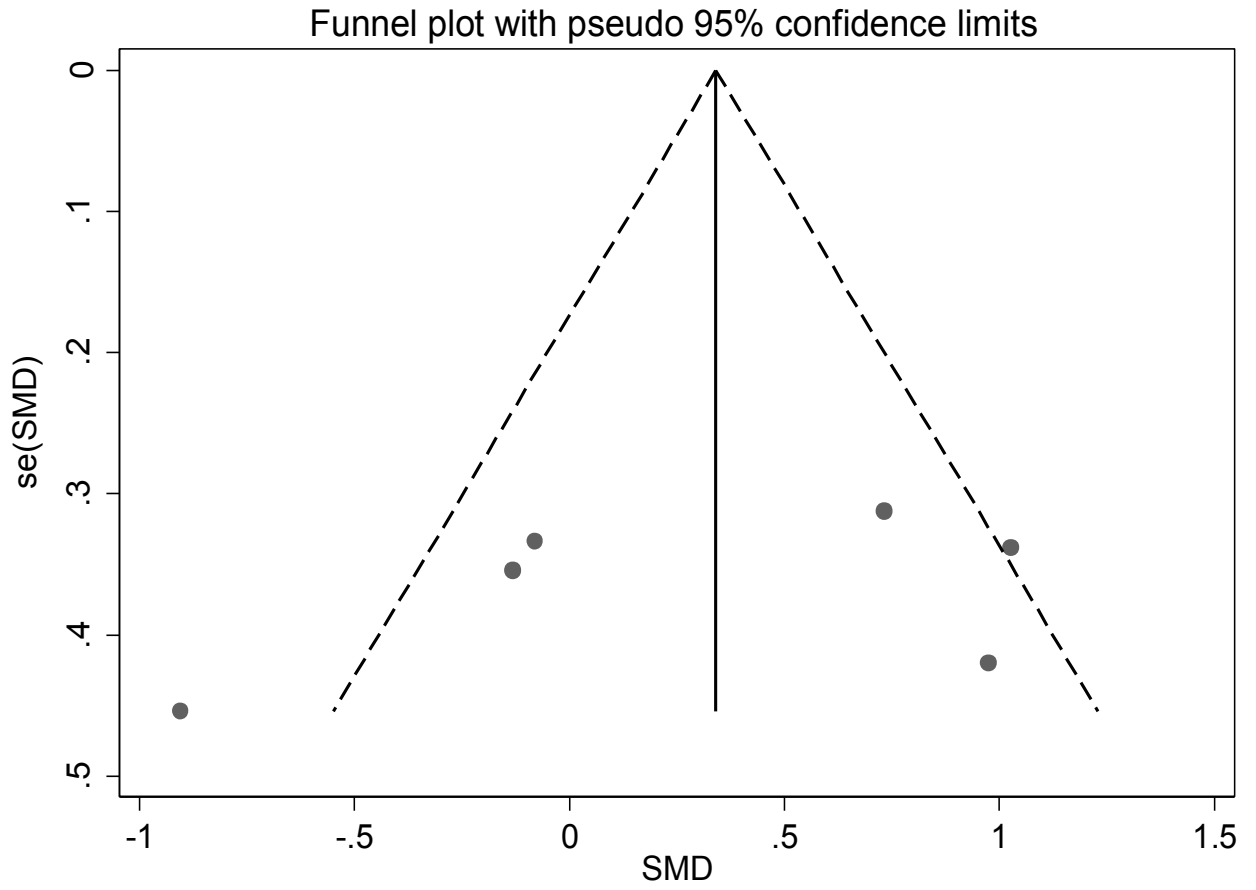
Were exercise sessions supervised (0.5 for partial supervision)	Were dropouts reported?	Were data presented for primary and secondary outcome measures?	Did the analysis include an intention to treat analysis?	Were adverse events reported?	Total quality score (out of 10)
1.0	1.0	1.0	0.0	1.0	8.0
1.0	1.0	1.0	0.0	1.0	8.0
1.0	1.0	1.0	1.0	1.0	9.5
1.0	1.0	1.0	0.0	1.0	8.0
1.0	1.0	1.0	0.0	0.0	6.5
1.0	1.0	1.0	0.0	1.0	8.0
0.5	1.0	1.0	0.0	0.0	5.5

(<<<continued)

Electronic Supplementary Material, Figure S1. Funnel plot assessing the symmetry of the standardized mean difference in muscular strength outcomes between the treatment and control groups



Electronic Supplementary Material, Figure S2. Funnel plot assessing the symmetry of the standardized mean difference in total body muscle mass between the treatment and control groups

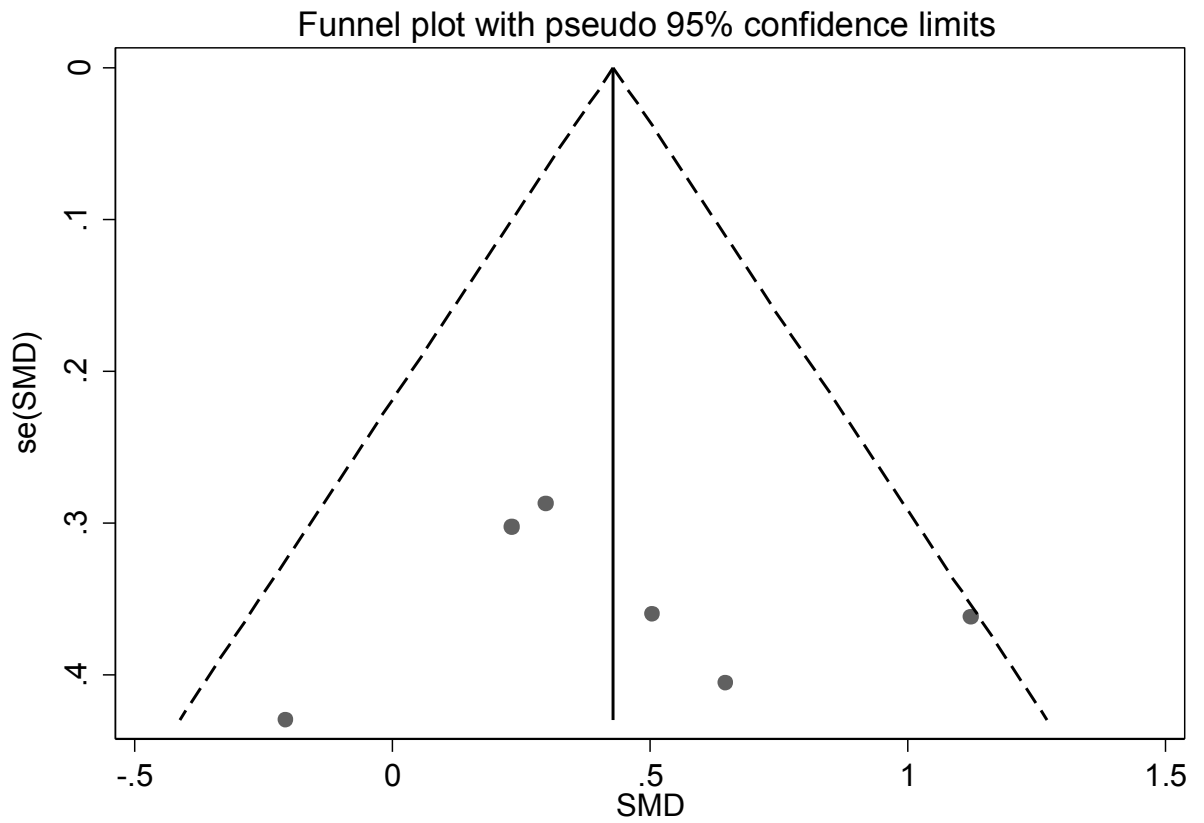


Electronic Supplementary Material, Table S3. Sensitivity analysis of randomized controlled trials investigating total body muscle mass outcomes

	N studies	N sample	SMD	LCL	UCL	P-value	I ²	p-value
Fixed effects model	6	200	0.34	0.05	0.63	0.02	73.5	0.002
Exclusion of 1 study of lower quality (score <6.0)	6	200	0.29	-0.27	0.86	0.311	73.5	0.002
Exclusion of 1 study involving PRT + nandrolone decanoate	5	168	0.38	-0.28	1.03	0.26	76	0.002
Exclusion of 2 studies in cohorts >60 yr	4	130	0.01	-0.74	0.76	0.98	77.1	0.004
Exclusion of 1 study in South Korea (and measuring BIA)	5	160	0.14	-0.46	0.74	0.651	71	0.008
Exclusion of 1 study in non-dialysis CKD	5	174	0.17	-0.46	0.79	0.602	75.4	0.003
Exclusion of 2 studies on PRT + diet	4	152	0.39	-0.17	0.96	0.171	66.2	0.031
Exclusion of 3 studies of longer duration	4	134	0.43	-0.2	1.06	0.18	68.8	0.022
Exclusion of 3 studies prescribing PRT during dialysis time	3	88	0.39	-0.78	1.56	0.515	84.9	0.001

SMD=standardized mean difference, LCL=lower confidence interval, UCL=upper confidence interval

Electronic Supplementary Material, Figure S3. Funnel plot assessing the symmetry of the standardized mean difference in lower body muscle hypertrophy measures (i.e. leg mass, or mid-thigh or quadriceps CSA) between the treatment and control groups



Appendix 3. Letter for doctor clearance

Dr.....
Level 9 East Wing,
CNARTs
Royal Adelaide Hospital
North Terrace
Adelaide, SA 5000

Dear Dr.....,

As part of the medical screening process for the research study entitled “**Can thrice a week of resistance training during dialysis improve cardiovascular health and other outcomes in patients with kidney failure?**”, the following patients have had their medical records reviewed for contraindications to exercise by exercise physiologist Danwin Chan.

1 LAST NAME, First Name (MRN: XX-XX-XX, DOB: XX-XX-XXXX)

To further the medical screening process please complete the attached checklist for each of your patients and return these forms to me using internal mail to Hampstead Dialysis Centre. Your assistance is greatly appreciated.

As you are aware, the purpose of this study is to evaluate the effects of resistance training during haemodialysis sessions on several indicators of health status in patients with ESRD. The variables to be evaluated include arterial stiffness, endothelial progenitor cells, C-reactive protein, lipid profile, physical activity level and function, depression, and quality of life.

I am hopeful that you will recommend participation in this research study to all patients meeting eligibility requirements. Please feel free to contact me if you require further information about the study.

Sincerely,

Danwin Chan, AEP, Doctoral Student

Name of patient: LAST NAME, First Name (MRN: , DOB:)

Checklist of conditions and events, which would require temporary exclusion from study:

- Acute change in mental status or delirium
- Cerebral haemorrhage within the past 3 months
- Exacerbation of chronic inflammatory joint disease or osteoarthritis
- Eye surgery within the past 6 weeks
- Fracture in healing stage _____
- Hernia, symptomatic (abdominal or inguinal)
- Myocardial infarction or cardiac surgery within past 3 months
- Other acute illnesses or change in symptoms _____

- Proliferative diabetic retinopathy or severe non-proliferative retinopathy
- Pulmonary embolism or deep venous thrombosis within 3 months
- Soft tissue injury, healing _____
- Systemic infection _____
- Uncontrolled blood pressure (>180/100)
- Uncontrolled diabetes mellitus (FBS>14mmol/L)
- Uncontrolled malignant cardiac arrhythmia (ventricular tachycardia, complete heart block, atrial flutter, symptomatic bradycardia)
- Unstable angina (at rest crescendo pattern, ECG changes)
- Other _____

Practitioner Name: _____ Date: _____

Practitioner Signature: _____

Appendix 4. Participant information sheet



Government of South Australia
SA Health



Human Research Ethics Committee

Participant Information Sheet

Project Title: Can thrice a week of resistance training during dialysis improve cardiovascular health and other outcomes in patients with kidney failure?

This is a research project and you do not have to be involved. If you do not wish to participate, your medical care will not be affected in any way. Also, you may withdraw from the project at any time after you have commenced.

The research will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research, 2007.

This information sheet will allow you to understand what is involved in the study, so as to allow you to decide whether or not to take part. Please ask any questions if there is still anything you are not clear about.

Who is carrying out the study?

Mr Danwin Chan, (BHSci(Hons), AEP, ESSAM)

Email: 17164203@student.uws.edu.au; Mobile: 0402 819 342

You are invited to participate in this study conducted by Mr Danwin Chan, PhD candidate, School of Science and Health, University of Western Sydney. Mr Chan can be contacted with the above contact details. This study is in partnership with the Central Northern Adelaide Renal and Transplant Service.

What is the study about?

The purpose of the study is to determine whether a structured resistance exercise program, under the supervision of an exercise physiologist, affects arterial stiffness and physical function in haemodialysis patients.

What does the study involve?

Three testing sessions (week 0, 13, 26) to evaluate your vascular health and physical fitness will be performed. No invasive procedure is involved. Each testing session will be approximately one hour and is conducted by Mr Danwin Chan. You will need to be dressed in workout gear (e.g. shorts, t-shirt and running shoes) to perform the testing session. There will be a 12-week period of no-exercise during dialysis between the first and second testing. You are requested not to change your physical activity habit at this period. This is then followed by a 12-week program of resistance training. Participants will perform about 40 minutes of upper body and leg exercises during haemodialysis while exercises involving the fistula arm will be done 15 minutes just before haemodialysis. This will occur three times per week at your haemodialysis centre. Some

pictures and video may be taken during the sessions with your consent. You will be asked to sign an additional consent form if this is to occur. The third test session is then conducted after the exercise program. Samples of blood (45ml in total) for health markers are also collected while you are on dialysis at week 0, 13 and 26. Your vascular health, physical function, muscle strength will be assessed in a dialysis centre without involving any invasive procedure. Assessment of muscle strength will require a sustained level of physical exertion and may result in muscle soreness for a day or two. You will also be asked questions about your medical history, perception of quality of life, mood and physical activity. Transportation cost to the testing location will be covered.

A video may be made when you perform the exercise. The video will then be used to train other people on haemodialysis. We will include you only if you agree to be videotaped.

Will the study benefit me?

At your completion of the exercise program, it is expected that your muscle strength, ability to carry out day-to-day tasks and sense of well being will improve. However, these benefits are by no means assured as individuals may react differently to the exercise stimulus.

What are the possible risks and discomfort of participating?

As with any exercise, injury or adverse event may result but this can be avoided with the investigator's and nurses' supervision and precautions. We thus believe the risk is very small to you. In addition, weight training in older adults, people with chronic diseases and patients on haemodialysis has been proven to be safe and has many health benefits.

There are minimal risks and discomfort associated with participation in this study, as summarized below:

1. There may be some changes in blood pressure, pulse and blood flow during dialysis due to the exercise, which will be closely monitored. It is anticipated that the nursing staff at the dialysis unit will be able to manage these quite easily.
2. Muscle strength testing may cause slight soreness over the next 1-2 days. Weight lifting exercises may cause fatigue, muscle soreness, injury to tendons or ligaments, or exacerbation of underlying arthritis or joint pain. Under direct supervision of an experienced trainer, such as will occur in this study, these complications are uncommon, and usually resolve quickly with modifications of the training regimen.
3. Blood samples will be drawn from your haemodialysis lines and thus will not cause additional pain.

How is this study being paid for?

You will not have to pay for any cost incurred in this study. Any additional tests, procedures, supervised weight training program and transportation cost for this study will be covered by the University of Western Sydney and Central Northern Adelaide Renal and Transplant Service.

Will anyone else know the results? How will the results be disseminated?

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or

except as required by law. Data from the study may be published in scientific/medical journal or be presented in a conference, but in a way that patients will not be identified. Data will be retained on file by the University of Western Sydney in a locked facility for a period of 5 years, after which time it will be destroyed in a confidential manner providing data analysis and reporting of results is complete. Study data will only be accessible to researchers involved in the study.

Can I withdraw from the study?

Participation is entirely voluntary: you are not obliged to be involved and if you do participate, you can withdraw at any time without giving any reason and without any consequences.

Your participation may also be ended prematurely for the following reasons:

4. The investigator feels that it is in your best interests to stop your participation
5. You have a kidney transplant or an unrelated medical illness or complication that makes study procedures unsafe or unreliable
6. The study, or part of the study, may also be stopped at any time at the discretion of the investigator or the researchers.
7. The study may also be stopped by the ethics committee who review the study to protect the rights and welfare of the study patients.

Can I tell other people about the study?

Yes, you can tell other people about the study by providing them with the chief investigator's contact details. They can contact the principal investigator to discuss their participation in the research project and obtain an information sheet.

What if I require further information?

When you have read this information, Mr Chan will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact Mr Chan via email or telephone; 17164203@student.uws.edu.au, mobile 0402 819 342.

What if I have a complaint?

This study has been approved by the Research Ethics Committees of both the University of Western Sydney (UWS) and Royal Adelaide Hospital (RAH). The RAH Protocol number is 120507 and the UWS project number is H9651.

If you have any complaints or reservations about the ethical conduct of this research, you may contact:

UWS Ethics Committee through the Office of Research Services
Tel: (02) 4736 0883 Fax: (02) 4736 0013 Email: humanethics@uws.edu.au.
and/or
Chairperson, Research Ethics Committee, RAH
Tel: (08) 8222 4139

Any issues you raise will be treated in confidence and investigated fully, and you will be

informed of the outcome.

Further enquiries should be directed to :

Mr Danwin Chan
PhD candidate / Exercise Physiologist
Hampstead Rehabilitation Centre
Hampstead Road, Northfield SA 5085

Phone: 08 8222 1500

Mr Robert Barnard
Chief Exercise Physiologist
Hampstead Rehabilitation Centre
Hampstead Road, Northfield SA 5085

Phone: 08 8222 1811

Dr Bobby Cheema
Head of Sport & Exercise Science Program
School of Science and Health (Campbelltown)
Penrith South DC, University of Western Sydney

Phone: 02 4620 3795

If you agree to participate in this study, you will be asked to sign the Participant Consent Form.

Appendix 5. Participant consent form



Government of South Australia
SA Health



Human Research Ethics Committee

Participant Consent Form

This is a project specific consent form. It restricts the use of the data collected to the named project by the named investigators.

Project Title: Can thrice a week of resistance training during dialysis improve cardiovascular health and other outcomes in patients with kidney failure?

Investigators: Mr Danwin Chan^{1,2}, Dr Birinder S. Cheema¹, Mr Robert Barnard², Dr Simon Green¹, Prof Maria Fiatarone Singh³

(¹University of Western Sydney, ²Centre for Physical Activity in Ageing, ³University of Sydney)

I,....., consent to participate in the research project titled "**Can thrice a week of resistance training during dialysis improve cardiovascular health and other outcomes in patients with kidney failure?**".

I acknowledge that:

I have read the participant information sheet [or where appropriate, 'have had read to me'] and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s and with a family member or friend.

The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

I understand that I may not receive any health benefit from taking part in this study.

I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.

I agree to truthfully answer all of the questions asked regarding my medical past. I agree to cooperate with the instructions for participating in this study as described above

I agree for my usual treating doctor to be contacted for relevant information as part of the study and that he/she will be asked to provide information about my suitability for inclusion in the exercise program.

I understand that my involvement is confidential and that the information gained during

the study may be published but no information about me will be used in any way that reveals my identity.

I understand that transportation to assessments will be provided. If I chose to use personal transportation, a reimbursement of \$20 will be provided for each day trip.

I understand that I can withdraw from the study at any time, without affecting my medical care or my relationship with the researcher/s now or in the future.

Participant's full name: _____
Participant's signature: _____ Dated: _____

I certify that I have explained the study to the participant/volunteer and consider that he/she understands what is involved.

Investigator's full name: _____
Investigator's signature: _____ Dated: _____

This study has been approved by the Research Ethics Committees of both the University of Western Sydney and the Royal Adelaide Hospital.

The RAH protocol number is: **120507**
The UWS project number is: **H9651**

If you have any complaints or reservations about the ethical conduct of this research, you may contact either:

Ethics Committee
Office of Research Services
University of Western Sydney
Tel: +61 2 4736 0229
Fax: +61 2 4736 0013
rah.ethics@health.sa.gov.au
Email: humanethics@uws.edu.au.

Research Ethics Committee
The Royal Adelaide Hospital
Tel: +61 8 82224139
Fax: +61 8 82223035
Email:

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

Appendix 6. Manual for arterial stiffness assessments

PULSE WAVE ASSESSMENT

EQUIPMENT

- Stopwatch or timer
- Alcohol swabs
- Surgical razor
- ECG electrodes
- Large bone calliper
- Fine tip marker
- Small stickers
- SphygmoCor unit with ECG leads
- Notebook computer with SphygmoCor software installed

Note: PWA = Pulse wave analysis; PWV = Pulse wave velocity

ORDER OF TESTING

1 Equipment Set-up

- Connect the SphygmoCor unit to the laptop via USB (use the bottom port, on the right of the laptop)
- Connect the ECG leads and footswitch to the SphygmoCor unit
- Connect the Laptop to the power and switch on.
- Log-in; Username: user - Password: sports, and open the SphygmoCor software.
- Enter patient details (see below)
- Enter study details (see below)

2 Patient Set-up

- Patient should be in a gown
- Check the patient is fasting, and consumed no caffeine
- Once the patient lies down for the first test of the morning (BIA), a stopwatch or timer should be used to ensure they are in the supine position for 10 minutes before commencing data collection.
- Place ECG electrodes and connect the leads in a II lead configuration (see below)

3 Data Collection

- Enter the diastolic and systolic blood pressure values that have been obtained from the cuff sphygmomanometer. Use the mean of two measures taken 1 min apart in the supine position
- Wait 2 minutes
- During the PWA data capture, use the tonometer to identify the brachial and posterior tibialis (PT) sites to be used in PWV – a site where a clear waveform can be observed should be selected
- Mark the brachial (fine tip marker), and PT (fine tip marker) sites
- Conduct PWA (see below)
- Check quality and repeat if necessary (see below)
- Remove the patient's pillow
- Measure the distances for PWV (see below)

- Conduct PWV (see below)
- Check quality and repeat if necessary (see below)
- Replace the patient's pillow
- Conduct HRV (see below)
- Remove ECG leads, close down the software and continue with the next assessment

PATIENT ENTRY - SELECT OR ENTER A NEW PATIENT

Open the 'Patient' screen by clicking on the '**Patient**' button. This screen will allow you to create a new patient entry or select a patient that is already present in the database.

To create a new patient entry, select the '**Create New**' button and enter the patient details. Once you have finished entering the patient details, click on the '**Update**' button to add the details of the patient to the database.

To select an existing patient from the database, you may choose the patient by **one** of the following means:

- Scroll down the list of patients and click on the row to select that patient. If you click on the heading 'Family name' at the top of the browser this will place the patients in alphabetical order. When the patient is selected the patient name is highlighted.

OR

- Place the cursor in the 'Patient Search' field and enter the patient's family name. Click the 'Search' button or press 'Enter' and the system will select the patient whose family name is the closest match. Ensure the patient you wish to select has been highlighted.

Note: Before creating a new patient entry, please check that the patient does not already exist in the database, as separate patient entries cannot be merged.

PULSE WAVE ANALYSIS (PWA) - ENTERING STUDY DETAILS

While still in the 'Patient Screen'; select '**PWA**' mode by clicking on the 'PWA' button on the left-hand side of the screen.

Open the Study Screen by clicking on the "**Study**". This screen will allow you to enter the study details and to proceed to 'Capture data'.

For measurements taken at the radial artery:

- Click the 'radial' check box.
- Enter the diastolic and systolic blood pressure values that have been obtained from the cuff sphygmomanometer. Use the mean of two measures taken 1 min apart in the supine position.
- The Medication, Notes, Operator and Anthropometric fields are optional.

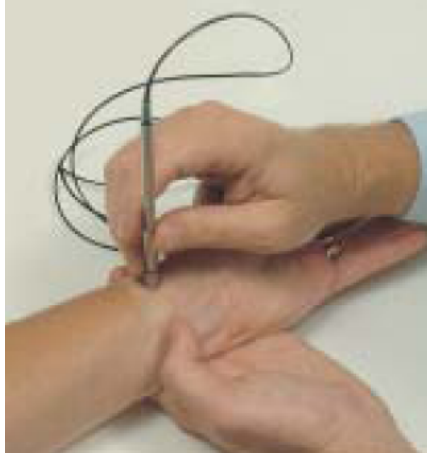
At least 2 minutes should elapse between taking the blood pressure and performing the tonometry reading.

PERFORMING THE DATA CAPTURE

To proceed to the capture data screen, click on the '**Capture Data**'.

Placement of the tonometer:

• Feel for the location of the strongest pulse at the radial artery of the patient’s right wrist, and place the tonometer on the skin at this point. The best results are obtained if the patient’s wrist is bent slightly downwards, in the ‘dorsiflex’ position. You may wish to support the patient’s wrist in your hand or place a small pillow or rolled towel under the patient’s wrist for support.



• Gently press the tonometer into the skin until a waveform signal appears on the screen. If the trace is off the screen, a straight line will be drawn across the horizontal axis of either the top or bottom of the signal screen, indicating that either too much or not enough pressure is being applied, respectively.

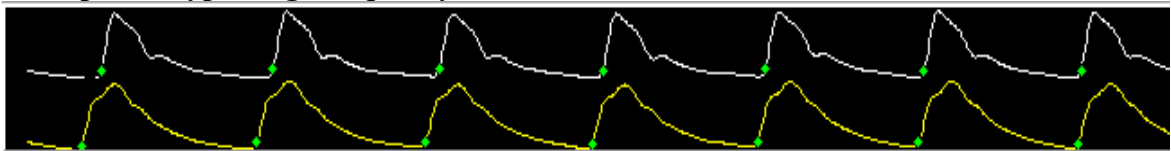
• The tonometer should be perpendicular to the wrist and adjustments to the position should be made until a strong, accurate and reproducible waveform is displayed in the ‘Signal detail’ window. This signal will be automatically re-scaled and zoomed to fit the waveform within the signal detail window every 5 seconds.

At this point you should identify the brachial and PT sites and lightly mark them in preparation for PWV testing. A sharp initial upstroke on each wave is most important for these sites rather than a large consistent waveform.

Capturing the waveforms:

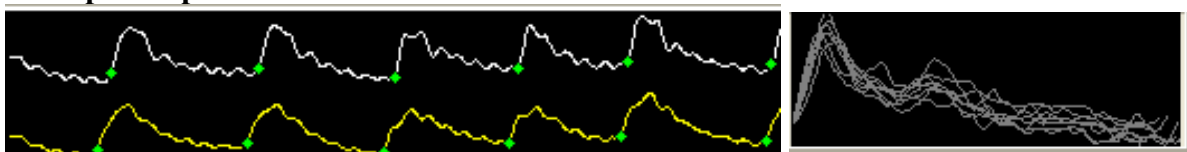
• **Once you have achieved a consistent radial pressure waveform,** hold steady for at least 12 seconds (equal to approximately 3 screen sweeps of waveforms) press the ‘Space Bar’ on your keyboard or press the foot switch.

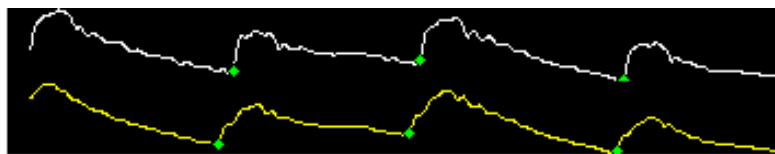
Examples of typical, good quality radial waveforms



Each waveform should have a sharp initial upstroke. The series of waveforms should have consistent peaks and troughs, and the contour of the waveform, in particular the peak pressure and shoulder, should be identical.

Examples of poor raw waveform data





EXAMINE THE REPORT FOR QUALITY CONTROL

After you have completed the data capture, the 'Report Screen' will be automatically displayed. This can also be recalled at any time by selecting the patient in the 'Patient Screen' and pressing the 'Report' button.

Operator Index

The main quality control parameter is the Operator Index. This is displayed on both the Clinical and Detailed Screen. The Operator Index is a number that is calculated from a weighting equation using four quality indices.

The Operator Index range is 0-100. As a general guide, **if the Operator Index is ≥ 80 it is considered acceptable**. If the Operator Index is ≤ 79 the recording is unacceptable and should be repeated.

PULSE WAVE VELOCITY - ENTERING STUDY DETAILS

While in the 'Patient Screen'; select **PWV** mode by clicking on the 'PWV' button on the left-hand side of the screen.

Open the Study Screen by clicking on the 'Study'. This screen will allow you to enter the study details and to proceed to 'Capture data'.




Mandatory fields to be selected or entered:

- Click in the box corresponding to the site from where the measurement is to be taken.
Site A is the brachial site at which the first measurement is to be taken and;
Site B refers to the PT site at which the second measurement will be taken.
- **Enter the blood pressure** (systolic and diastolic) that has been obtained from the cuff sphygmomanometer before PWA.
- The Capture Time is set to a default of 10 seconds for both the Site A and Site B measurements.

Measuring the Sites:

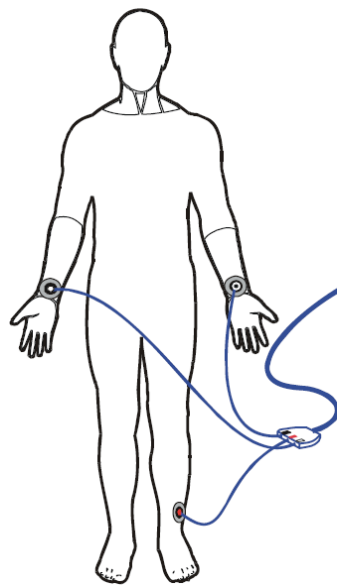
- The Distance should be measured on the right side and entered as the **distance to the nearest 1 millimetre directly between each artery location and the suprasternal notch** are entered in the proximal and distal boxes.
- Palpate for the supra-sternal notch and identify the point immediately superior to the sternum.
- With the patient standing upright in the anatomical position with the head facing straight, using a stadiometer:
- Measure and record the distance from the sternal notch to the floor (Figure 2).
- Measure and record the distance from the marked brachial site to the floor (Figure 3).
- Using a large bone caliper, measure and record the distance from the base of the foot to the marked posterior tibial site while the patient is lying supine – ensure

that the blade of the calliper runs along the length of the foot and that the foot is dorsi flexed to 90° (Figure 4).

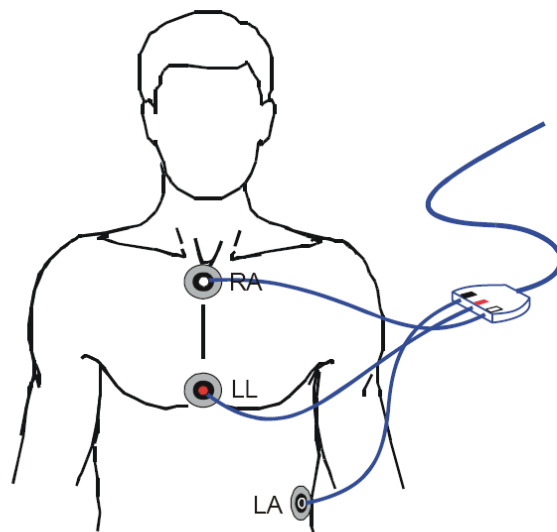
		
<p>Figure 2. Sternal notch height Rest corner of the stadiometer on the sterna notch</p>	<p>Figure 3. Brachial height Bottom edge of stadiometer in line with marked site</p>	<p>Figure 4. Posterior tibialis height Distance from the base of the foot to the marked posterior tibialis site</p>

Placement of ECG leads:

To ensure a stable, artefact free ECG, the skin should be properly prepared (hair removed at electrode site and skin cleaned with an alcohol wipe), and the electrodes positioned correctly. The ECG leads should be positioned as shown in the diagram. This is a Lead II configuration. The leads can be placed either on the limbs or on the chest area if required for stronger QRS levels).



Electrodes on Peripheral Limbs



Electrodes on Chest

To proceed to the capture data screen, click on the ‘**Capture Data**’.

Once the ECG trace is visible on the screen and is steady, proceed as follows:

- Check that the R wave on the ECG trace is the tallest part of each ECG waveform, noting that this may require adjustment of the ECG cables or ECG electrodes.

- **The tonometer should be placed at the artery defined for Site A (brachial)**. A strong, accurate and reproducible waveform should have already been identified during PWA at the marked site.

This signal will be automatically re-scaled and zoomed to fit the waveform within the signal detail window every 5 seconds.

- **When you are satisfied that you have a good reading**, press the ‘**Space Bar**’ on your keyboard or click the footswitch.

- A prompt window will appear confirming that the signals have been captured successfully.

When you are ready to proceed to take the reading at Site B, click the OK button or press the footswitch. If you wish to take the reading again, click No and repeat the reading at Site A.

- **Repeat the process by placing the tonometer on the artery defined for Site B (PT)** and proceed with the capture when you have obtained a signal of satisfactory quality. A prompt box will appear to confirm that the signal was captured successfully. If you are satisfied with the reading at Site B and wish to proceed to the report, click OK. If you wish to repeat the reading at Site B, click No and repeat the reading at Site B.

EXAMINE THE REPORT FOR QUALITY CONTROL

After you have completed the data capture, the Report Screen will automatically be displayed. This can also be recalled at any time by selecting the patient in the Patient Screen and pressing the ‘Report’ button.

Check that information was entered correctly on the Study Screen. If the patient data is incorrect, click the patient tool-bar button to return to the Patient Screen and update patient details. If the study data is incorrect, click the ‘Recalculate’ tool-bar button to open the SphygmoCor Recalculate Report window.

Quality Control checks:

- The tonometry waveforms should be clear and smooth and it is important that the foot of the waveform is easily identified. The quality control parameters used in PWA may assist in assessing the quality of the tonometry waveform and are displayed to the right of the waveforms.

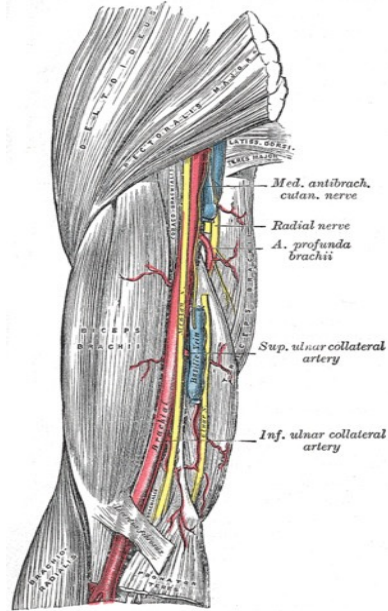
- The green dots on the waveforms indicate the marker for calculating timing from the waveform to the ECG (onset points) and it is important that these are in a similar location on each waveform.

- The R wave on the ECG should be the tallest part of the ECG trace and the green dots should be located at the top of the R wave and not on any other part of the ECG trace.

- **The SD(ms) in the statistical table** (i.e. for each of the site A and B measures) should be below 6% of the mean time. **If the SD is above 6% it will appear in red.** Repeat the reading.

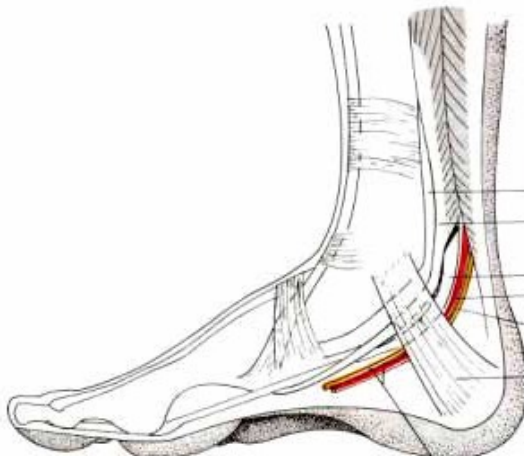
Additional comments on performing brachial and posterior tibial measurements:

Brachial Measurement:



The operator should feel for the position for the strongest pulse at or above the bicipital aponeurosis, medial to the biceps tendon, and place the tonometer directly on the top of the skin at this point. The operator can be standing or seated to one side. A pillow may be placed next to the patient to allow the operator to rest their forearm to ensure that the tonometer and wrist remain steady during the measurement. On leaner subjects a clearer pulse wave may be observed at a slightly more proximal site.

Posterior Tibial Measurement:



The operator should feel for the position for the strongest pulse. The posterior tibial artery pulse can be palpated posterior and inferior to the medial malleolus. The pulse wave can generally be obtained with the foot resting at a natural angle, but on certain individuals a better wave form may be obtained with either the foot in neutral (perpendicular to the bed), or with slight external rotation and passive dorsi flexion provided by the operator.

VARIABLES

A description of all variables for PWA, PWV can be found in the SphygmoCor clinical guides.

COPYING A DATABASE

Copying a database is a method to backup or transfer databases from one computer to another.

To Copy the selected database:

Step 1. Select the database you want to copy.

Step 2. Click the Copy button. The “Copy To” dialog window opens.

Step 3. Select the Windows folder that you want to copy the database to, and click the Ok button. The selected database is then copied to the folder you selected.

CAUTION

When copying a database, ensure that you don't select a location where any database already exists. If this occurs, the database will be corrupted and the records will not be recoverable.

EXPORTING DATA

You can export data from the SphygmoCor system for use in other programs. Data is exported in a Tab-delimited text-file format. This format is easy to import into spreadsheet applications, such as Statview or Excel.

DATABASE WARNING

Do not open the SphygmoCor database with Microsoft Access or any other program as it may corrupt your data. All database interactions should be performed using the SphygmoCor software. For further advice contact AtCor Medical Product Support.

Whenever you export data, the Export window is displayed: This window allows you to specify where the data will be exported to, in the Windows folder structure and what the file will be called. The comment in the central section of the window changes according to which of the export operations is being performed.

EXPORT ALL MEASUREMENTS IN THE DATABASE

Step 1. Click the Export option on the System>Database menu. You must be in the Patient screen to do this. The Export window opens

Step 2. Use the Select button to choose the Windows folder and/or file name to which you want all the measurements exported.

Step 3. Click the Export button. A progress bar shows you how much of the export has been completed. At the end of the operation, a status message appears in the Export window:

Step 4. Click the Close button to close the Export window.

A separate export process must be performed for each study database, as well as for each PWA and PWV datasets (i.e. two exports per study).

Appendix 7. Protocol for 3 repetition-maximum strength test

(Modified from Baechle et al, 2008 p.396)

1. Instruct the participant to warm up with a light resistance that easily allows 5 to 10 repetitions.
2. Provide a 1 minute rest period.
3. Estimate a warm-up load that will allow the participant to complete 5 to 7 repetitions by adding 4 – 9 kg for unilateral lower body exercise.
4. Provide a 2 minutes rest period.
5. Estimate a conservative load that will allow the participant to completed 3 to 5 repetitions by adding 4 – 9 kg for unilateral lower body exercise.
6. Instruct the participant to attempt a 3RM.
7. If the participant was successful, provide a 2 minutes rest period and go back to step 5.
8. If the participant failed, provide a 2 minutes rest period, then decrease the load by subtracting 2 – 4 kg for lower body exercise. Return to step 6.
9. Continue increasing or decreasing the load until the participant can complete 3 repetitions with proper technique. Ideally, the participant's 3 repetitions maximum will be measured within 3 to 5 testing sets.

Reference:

Baechle, TR, Earle, RW & Wathen, D. 2008, 'Resistance training', in *Essential of strength training and conditioning, 3rd edn*, ed. TR Baechle & RW Earle, Human Kinetics, Champaign, Illinois.

Appendix 8. Protocol for 6-minute walk

Equipment: Cones/markers, Measure wheel, Stopwatch

Site: Non-slippery, flat surface outdoor/indoor area with shelter

Preparation:

1. Set up the cones according to the figure below by measuring a 20 x 2 metres rectangular area using the measure wheel. The cones should be 5 metres apart from each other.
2. Ensure that participant is wearing appropriate footwear and that no hindering object is on the designated walking area. Remove any if there is.
3. Before beginning, instruct the participant to walk as fast as he can around the cones to cover as much ground as possible in six minutes. The pace should be within the participant's comfort zone and he must not run. Inform the participant he is allowed to rest if necessary but should continue as soon as they are able to. However, if participants feel dizzy, pain, angina, nauseous or undue fatigue, the test will be discontinued.
4. Inform the participant you will say, "Ready, Go!", then the participant should begin walking immediately and you will start the timer at the same time. Begin when the participant is ready.
5. No verbal encouragement was given during the test but feedback regarding the remaining time is to be given every two minutes and when 1 minute is left.

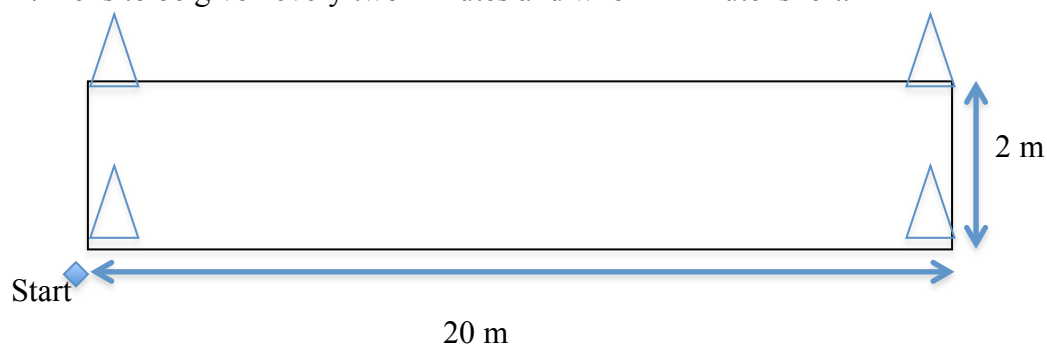


Figure. 20 by 2 metres walking circuit with cones marking the corners.

6. The tester will measure the total distance walked to the nearest 0.5 metres using a measure wheel. Record the distance in the participant's case report form.
7. At the end of the test, accompany the participant to walk slowly around for a minute to cool down.

Appendix 9. Protocol for waist circumference measure

Equipment: Non-metallic tape measure with a spring-load handle

Preparation:

1. With the participant's waist uncovered, he stands upright with arms relaxed at the sides.
2. Take the horizontal measure, mid point between the lower costal (rib) border and iliac crest. The measurement is taken at the end of a normal expiration.
3. The tape should be placed on the skin surface without compressing the subcutaneous adipose tissue
4. The spring loaded handle of the tape measure should be extended to the same marking with each trial.
5. Two duplicate measures need to be done. If the measurements are not within 5 mm, retest the measurements till they are. Record the measurements and take the average of the last two measures.

Risk level based on waist circumference in general population adults :

	Waist Circumference (cm)	
	Females	Males
Risk category		
Very low	<70	<80
Low	70-89	80-99
High	90-109	100-120
Very High	>110	>120

Reference:

American College of Sports Medicine. Guidelines for exercise testing and prescription. Philadelphia: Lippincott Williams & Wilkins; 2006, pp 58-61

Norton, K & Old, T. Anthropometrica. Sydney: UNSW Press; 2002, pp 58

Appendix 10. Case report form

CASE REPORT FORM

Age:

Research ID Number:

MRN:

(Circle)

Baseline / 13 weeks / 26 weeks

Date:

Demographic Information

	Patient details	Person for Notification
Name		Relationship
Address		
Telephone		H: W:

Gender: Male / Female

Ethnic:

- Caucasian
- Asian
- Aboriginal
- Middle East
- Black
- Indian
- other _____

Marital Status:

- married / defacto
- widowed
- divorced
- single/ never married
- separated

Residence

In what type of accommodation do you live?

- house (own)
- house (rented)
- unit (own)
- unit (rented)
- retirement village
- hostel
- nursing home
- board/rooming house

How long have you lived at this address?

Years _____ Months _____

Living Situation

With whom do you live?

- alone
- spouse / partner
- family
- paid carer
- friend
- other residents

Total number of persons in the household

_____ people

Education

What is the highest grade or year of school you completed?

- never /kindergarten 0
- primary school 1 2 3 4 5 6
- high school 7 8 9 10 11
- tertiary 12
- post graduate 13 14 15 16
17 18 19 20

Work

Do you currently work for pay either for yourself or someone else?

- yes
- no

How many hours per week do you work for pay?

_____ hours / week

Do you currently work as a volunteer?

- yes
- no

How many hours volunteer hours / week do you work?

_____ hours / week

Annual income

In what range is your annual income?

- < \$ 15,000
- \$ 15,000- \$30,000
- >\$30,000

Pension

Do you receive a pension?

- Nil
- DVA
- Age pension
- Widows pension
- Disability Pension

Hospital admissions

During the past 12 months, how many different times did you stay in hospital over night?

_____ number of times

_____ number of days in hospital

Smoking

Are you a non-smoker, ex-smoker or current smoker?

- Non-smoker
- Ex-smoker
- Current smoker

If you are an ex-smoker, how many years has it been since you quit?

_____ years

If you are an ex-smoker or current smoker, how many cigarettes, cigars or pipes did/do you smoke on an average day?

_____ per day

20 cigarettes =1 pack

Alcohol

During the past 7 days, what was the average number _____ standard drinks/day of standard drinks of alcoholic beverages you had drunk per day?

Comments:

Subject Medical History

Primary Cause of Renal Failure:

- Glomerulonephritis
- Hypertensive nephrosclerosis
- Analgesic nephropathy
- Polycystic kidney disease
- Diabetic nephropathy
- IgA nephropathy
- Lupus/SLE
- Reflux nephropathy/ chronic pyelonephritis
- Aetiology uncertain
- Other: _____

Haemodialysis:

- Date commenced HD: _____
- Duration of HD (yr & months): _____
- Problems with dialysis over past 6 months:
 - Hypotension
 - Hypertension
 - Arrhythmias (type): _____
 - Fistula access problems: _____
 - Subjective symptoms during session: _____
 - _____
 - Laboratory abnormalities: _____
 - Other: _____

- Kt/V (Date, Value): _____

Other Diagnoses:

- Active malignancy:
 - Type: _____

- Gastrointestinal disease:
 - Type: _____

- History of M.I:
 - Date: _____
- History of Cardiac Surgery:
 - Type: _____
 - Date: _____
- History of Hernia Repair:
 - Date: _____
- Alcohol or Drug Dependency

Current Level of Physical Activity:

- **Aerobic Exercise:**
 - Frequency: _____
 - Intensity: _____
 - Modality: _____
- **Resistance Exercise:**
 - Frequency: _____
 - Intensity/Sets/Reps: _____
 - Modality: _____
- **Other:** _____

History of exercise related Injuries (specify): _____

Comments:

Anthropometric Measures

Measurements	Measure 1	Measure 2	Measure 3	Mean/Median
Weight (kg)				
Height (cm)				
BMI (kg/m ²)				
Waist circumference (cm)				

Arterial Stiffness (Baseline / 13 Weeks / 26 Weeks)

All measurements performed on the right side left side, reason: _____

Measurement (mm)	Participant preparation
Sternal notch height	Prior 4 hours of fast from food & caffeine <input type="checkbox"/>
Brachial artery height Initial Measure, Difference in initial and final measures FINAL distance	12 hours since last exercise of any kind except simple walking <input type="checkbox"/>
Posterior tibialis artery height (Dorsal pedis if used)	Loose clothing with short sleeves <input type="checkbox"/>
Distance (Brachial → Sternal)	10 minutes of supinated rest prior to testing <input type="checkbox"/>
Distance (Post. Tibial → Sternal)	

Date: _____

Time: _____

Measurement	Result	Comments
Supine brachial blood pressure (mmHg)	Test 1: Test 2: Average:	
Observed Augmentation Index		Operation Index Trial 1: _____ <input type="checkbox"/> > 80, <input type="checkbox"/> < 80 repeat Trial 2: _____ <input type="checkbox"/> > 80, <input type="checkbox"/> < 80 repeat Trial 3: _____ <input type="checkbox"/> > 80, <input type="checkbox"/> < 80 repeat
Normalised Augmentation Index		
Observed PWV (m/s)		Quality Control 1) either SD red(redo) <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 2) ECG-proximal <small>green</small> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> 3) ECG-distal <small>green</small> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Normalised PWV (m/s)		

Comments: _____

Six Minute Walk Test (Baseline / 13 Weeks / 26 Weeks)

Distance (m): _____

Comments: _____

Isometric Strength (Baseline / 13 Weeks / 26 Weeks)

Measurement (kg)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Final Score
Right Handgrip						
Left Handgrip						
Right Leg press (3RM)						
Left Leg press (3RM)						

Code each test in the comments column of table by using the format below:

- 1= Protocol completed
- 2= Not completed due to death
- 3= Not completed due to refusal, drop-out or loss to follow up
- 4= Not completed due to medical illness or incapacity
- 5= Not completed due to equipment failure or examiner error
- 6= Not completed due to other cause (specify)

Comments: _____

SF-36 Health Status Survey (Baseline / 13 Weeks / 26 Weeks)

Date: _____

This survey asks you your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. In general, would you say your health is:
1. Excellent
 2. Very Good
 3. Good
 4. Fair
 5. Poor

2. Compared to one year ago, how would you rate your health in general now?
1. Much better now than 1 year ago
 2. Somewhat better now than 1 year ago
 3. About the same as 1 year ago
 4. Somewhat worse now than 1 year ago
 5. Much worse now than 1 year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Activities	Yes, Limited A Lot	Yes, Limited A Little	No, Limited At All	Not At
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3	
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3	
c. Lifting or carrying groceries	1	2	3	
d. Climbing several flights of stairs	1	2	3	
e. Climbing one flight of stairs	1	2	3	
f. Bending, kneeling or stooping	1	2	3	
g. Walking more than a mile	1	2	3	
h. Walking several blocks	1	2	3	
i. Walking one block	1	2	3	
j. Bathing or dressing yourself	1	2	3	

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely

7. How much bodily pain have you had during the past 4 weeks?

1. None
2. Very mild
3. Mild
4. Moderate
5. Severe
6. Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

1. Not at all
2. A little bit
3. Moderately
4. Quite a bit
5. Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks....

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little Bit of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.)?

1. All of the time
2. Most of the time
3. Some of the time
4. A little of the time
5. None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Geriatric Scale

(Baseline / 13 Weeks / 26 Weeks)

Date: _____

Choose the best answer for how you have felt in the past week (7 days):

- | | | YES | NO |
|--|-----|--------------------------|--------------------------|
| 1. Are you basically satisfied with your life? | 1. | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Have you dropped many of your activities and interests? | 2. | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Do you feel that your life is empty? | 3. | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Do you often get bored? | 4. | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Are you hopeful about the future? | 5. | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Are you bothered by thoughts you can't get out of your head? | 6. | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Are you in good spirits most of the time? | 7. | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Are you afraid something bad is going to happen to you? | 8. | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Do you feel happy most of the time? | 9. | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Do you often feel helpless? | 10. | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Do you often get restless and fidgety? | 11. | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Do you prefer to stay at home, rather than going out and doing new things? | 12. | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Do you frequently worry about the future? | 13. | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Do you feel you have more problems with memory than most? | 14. | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. Do you think it is wonderful to be alive now? | 15. | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Do you often feel downhearted and blue? | 16. | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Do you feel pretty worthless the way you are now? | 17. | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Do you worry a lot about the past? | 18. | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. Do you find life very exciting? | 19. | <input type="checkbox"/> | <input type="checkbox"/> |
| 20. Is it hard for you to get started on new projects? | 20. | <input type="checkbox"/> | <input type="checkbox"/> |
| 21. Do you feel full of energy? | 21. | <input type="checkbox"/> | <input type="checkbox"/> |
| 22. Do you feel that your situation is hopeless? | 22. | <input type="checkbox"/> | <input type="checkbox"/> |
| 23. Do you think that most people are better off than you are? | 23. | <input type="checkbox"/> | <input type="checkbox"/> |
| 24. Do you frequently get upset over little things? | 24. | <input type="checkbox"/> | <input type="checkbox"/> |
| 25. Do you frequently feel like crying? | 25. | <input type="checkbox"/> | <input type="checkbox"/> |
| 26. Do you have trouble concentrating? | 26. | <input type="checkbox"/> | <input type="checkbox"/> |
| 27. Do you enjoy getting up in the mornings? | 27. | <input type="checkbox"/> | <input type="checkbox"/> |
| 28. Do you prefer to avoid social gatherings? | 28. | <input type="checkbox"/> | <input type="checkbox"/> |
| 29. Is it easy for you to make decisions? | 29. | <input type="checkbox"/> | <input type="checkbox"/> |
| 30. Is your mind as clear as it used to be? | 30. | <input type="checkbox"/> | <input type="checkbox"/> |

Record number of answers:

Physical Activity Scale for the Elderly (Baseline / 13 Weeks / 26 Weeks)

© New England Research Institute

LEISURE TIME ACTIVITIES

1. Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV or doing handcrafts?

[0] never
↓
Go to Q.2

[1] seldom
(1-2 days)
↓

[2] sometimes
(3-4 days)
↓

[3] often
(5-7 days)
↓

1a. What were these activities?

1b. On average, how many hours per day did you engage in these sitting activities?

[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example for fun or exercise, walking to work, walking the dog etc?

[0] never
↓
Go to Q.3

[1] seldom
(1-2 days)
↓

[2] sometimes
(3-4 days)
↓

[3] often
(5-7 days)
↓

2a. On average, how many hours per day did you spend walking?

[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

- b) On average, over the past 7 days, how many kms/miles/blocks have you walked?
(1 mile = 12 blocks: 1km = 0.625miles).

Number of blocks _____, or km _____, or miles _____ .

[1] less than 1 mile
[2] One but less than 2 miles
[3] two to 4 miles
[4] more than 4 miles

3. Over the past 7 days, how many flights of stairs have you climbed **up**? (one flight = 10 steps) Number of steps _____, or flights of steps _____.
- [1] less than 1 flight
 - [2] One but less than 2 flights
 - [3] two to 4 flights
 - [4] more than 4 flights

4. Over the past 7 days, how often did you engage in light sport or recreational activities such as lawn bowls, bowling, water aerobics, golf with a cart, yoga, tai chi, fishing from a boat or pier or other similar activities?

- [0] never
↓
- [1] seldom
(1-2 days)
↓
- [2] sometimes
(3-4 days)
↓
- [3] often
(5-7 days)
↓

Go to Q.5

4a. What were these activities?

4b. On average, how many hours per day did you engage in these light sport or recreational activities?

- [1] less than 1 hour
- [2] 1 but less than 2 hours
- [3] 2 – 4 hours
- [4] more than 4 hours

5. Over the past 7 days, how often did you engage in moderate sport or recreational activities such as doubles tennis, ballroom dancing, golf without a cart, softball or other similar activities?

- [0] never
↓
- [1] seldom
(1-2 days)
↓
- [2] sometimes
(3-4 days)
↓
- [3] often
(5-7 days)
↓

Go to Q.6

5a. What were these activities?

5b. On average, how many hours per day did you engage in these moderate sport or recreational activities?

- [1] less than 1 hour
- [2] 1 but less than 2 hours
- [3] 2 – 4 hours
- [4] more than 4 hours

6. Over the past 7 days, how often did you engage in strenuous sport and recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross country) or other similar activities?

- [0] never
↓
- [1] seldom
(1-2 days)
↓
- [2] sometimes
(3-4 days)
↓
- [3] often
(5-7 days)
↓

Go to Q.7

6a. What were these activities?

6b. On average, how many hours per day did you engage in these strenuous sport or recreational activities?

- [1] less than 1 hour
- [2] 1 but less than 2 hours
- [3] 2 – 4 hours
- [4] more than 4 hours

7. Over the past 7 days, how often did you any exercise specifically to increase muscle strength and endurance such as lifting weights or pushups etc?

- [0] never [1] seldom (1-2 days) [2] sometimes (3-4 days) [3] often (5-7 days)
- ↓ ↓ ↓ ↓

Go to Q.8

7a. What were these activities?

7b. On average, how many hours per day did you engage in exercise to increase muscle strength and endurance?

- [1] less than 1 hour [2] 1 but less than 2 hours
 [3] 2 – 4 hours [4] more than 4 hours

HOUSEHOLD ACTIVITIES

8. During the past 7 days, have you done any light housework such as dusting or washing dishes?

- [1] No [2] Yes

9. During the past 7 days, have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows or carrying wood?

- [1] No [2] Yes

10. During the past 7 days, did you engage in any of the following activities?

Please answer Yes or No and give the total time over the past 7 days spent engaging in the activities.

	No	Yes	Hours/wk
a. Home repairs like painting, wallpapering, electrical etc	1	2	
b. Lawn work or yard care including snow or leaf removal, wood chopping etc	1	2	
c. Outdoor gardening	1	2	
d. Caring for another person such as a dependent child, dependent spouse or another adult	1	2	

WORK-RELATED ACTIVITIES

11. During the past 7 days did you work for pay or as a volunteer?

[1] No [2] Yes



11a. How many hours per week did you work for pay and/or as a volunteer?
_____ hrs/wk

11b. Which of the following categories best describes the amount of physical activity required on your job and /or volunteer work?

- (1) Mainly sitting with light arm movements (eg. Office work, watch maker, seated assembly line worker, bus driver etc)
- (2) Sitting or standing with some walking (eg. Cashier, general office worker, light tool and machinery worker)
- (3) Walking with some handling of materials generally weighing less than 50 pounds (eg. Mailman, waitress, construction worker, heavy tool and machinery worker)
- (4) Walking and heavy manual work often requiring handling of materials weighing over 50 pounds (eg. Lumberjack, stone mason, farm or general labourer).

PASE Score

PASE Activity	Score	PASE weight	PASE score
Muscle strength/endurance*	h/d	30	
Strenuous sports*	h/d	23	
Moderate sports*	h/d	23	
Light sports*	h/d	21	
Job involving standing/walking*	h/d	21	
Walking*	h/d	20	
Lawn work or yard care		36	
Caring for another person		35	
Home repairs		30	
Heavy housework		25	
Light housework		25	
Outdoor-gardening		20	
PASE Total			

* determine the average number of hours/day (h/d) over a 7-day period

1= engaged in activity during the previous 7 days

0= did not engage in activity during the previous 7 days

Paffenberger Score

Blocks walked/wk	X	4 kcal / block	=	kcal
Flights climbed/wk	X	8 kcal / flight	=	kcal
Minutes light sport/recreation/wk	X	5 kcal / min	=	kcal
Minutes moderate sport/recreation or muscle strength/wk	X	7.5 kcal / min	=	kcal
Minutes heavy sport/recreation/wk	x	10 kcal / min	=	kcal
total				kcal / week

Comments :

- protocol completed
- not completed due to death
- not completed due to refusal, drop-out or loss to follow-up
- not completed due to medical illness or incapacity
- not completed due to examiner failure or error
- not completed due to other : _____

Appendix 11. Weekly Status Check

Study ID # _____

Date: _____

Week #: _____

Interviewer: _____ Telephone ___ In-person ___

During the past week have you had any of the following?

	Yes	No
1. Acute illnesses Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
2. Change in medication (prescribed, over-the-counter, herbal, nutritional supplement) Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
3. Visits to a health care professional Kind _____ Indication _____ Treatment _____	<input type="checkbox"/>	<input type="checkbox"/>
4. New physical, mental, or emotional symptoms of any kind Describe: _____	<input type="checkbox"/>	<input type="checkbox"/>
5. Falls Number _____ Circumstance(s) _____	<input type="checkbox"/>	<input type="checkbox"/>
Injury _____	<input type="checkbox"/>	<input type="checkbox"/>
6. Have you attended all exercise sessions? If not, number attended _____ Reason for missed session(s) _____	<input type="checkbox"/>	<input type="checkbox"/>
8. Other Questions or Comments of subject: _____ _____		

Comments :

- protocol completed
 - not completed due to death
 - not completed due to refusal, drop-out or loss to follow-up
 - not completed due to medical illness or incapacity
 - not completed due to examiner failure or error
- not completed due to other : _____

Appendix 12. Protocol for exercise intervention



Seated Bicep Curl with dumbbell

This exercise strengthens the upper arm muscles which flex the elbow.

1. Sit erect and towards the front of the chair. Hold a dumbbell at the side, and the palm of your hand facing forward.
2. Lift the dumbbell towards the shoulder by bending at elbow.
3. Lower the dumbbell slowly to the starting position.

Tips:

- Sit forward in the chair for this exercise to allow full ROM.
- Use the arm to move the weight – not the shoulder.
- Maintain good posture by sitting upright and not arching or slouching the back.



Seated Shoulder Press with dumbbell

This exercise strengthens the muscles of the shoulder and back of the upper arm which required to reach overhead.

1. Sit upright holding the dumbbell at shoulder level with palms facing forward.
2. Slowly lift the dumbbell so that it is over the head.
3. Lower the dumbbell following the same path and repeat.

Tips:

- Don't arch the back during the lift.
- Keep lifting arm close above the body when lifting or lowering the weights.



Seated Tricep Extension with dumbbell

This exercise will strengthen the muscles at the back of the upper arm which straighten out the elbow.

1. Sit upright and extend the arm straight up (pre-dialysis training), with the palms facing towards the body.
2. Slowly bend at elbow so that the elbow is lowered behind and slightly to the side of the head.
3. Return the dumbbell slowly to starting position.

Tips:

- Ensure the elbow stays as close to the ear as possible throughout the motion.

When training your fistula arm prior to dialysis, use your non-fistula arm to hold just below the elbow to help support the fistula arm throughout the exercise. During dialysis the trainer will support the training arm.



Seated Row with machine

This exercise will strengthen the muscles at the back of the upper torso needed to lift objects up or towards the body.

1. Sit upright with the back supported by the chair. The exercise machine's wheels should be locked prior to exercising.

2. Start with the arm extended away from the body with the palms facing down towards the floor.
3. Slowly pull back by bending at elbow back and to the side so that the elbow is slightly below the shoulder.
4. Return slowly to starting position.

Tips:

- Ensure the whole arm is always below shoulder level at all times when performing the action.
- Do not bend at the wrist to avoid placing undue strain on it.

Keep the legs on the leg rest to stable yourself.



Seated Chest Press with machine

This exercise will strengthen the muscles at the chest needed to push objects away from the body or the body off the floor.

1. Sit upright with the back supported by the chair. The theraband should be secured to the back of the chair.
2. Start with the arm bent, elbow to the side and with the palm facing down towards the floor. The theraband should be taut before beginning.
3. Slowly push forward by straightening at elbow fully before return slowing to starting position.

Tips:

- Ensure the whole arm is always below shoulder level at all times when performing the action.

Do not bend at wrist to avoid placing undue strain on it.



Seated Back Extension with elastic tubings

This exercise will strengthen the muscles at lower backed needed to stand up straight.

1. Sit leaning forward towards the knee on the chair but still keeping the back straight as much as one can. The elastic tubing was wrapped around the upper back and below the armpits with the exercise physiologist holding the elastic tubing in front.
2. Secure the theraband and keep it taut at the beginning position.
3. Sit back before returning to the earlier position.

Tips:

- Ensure the spine remain close to neutral position when bending forward and backward.



Leg press with machine

This exercise strengthens the muscles that are required to stand up from a chair.

1. Put both feet on the lower leg rest of the machine, shoulder width apart.
2. Push forward with both feet and straighten your legs.
3. Slowly return to original position.

Tips:

If the maximum weight available on the machine is too light, use single leg to do the exercise and start with a weight about as heavy as the maximum weight.



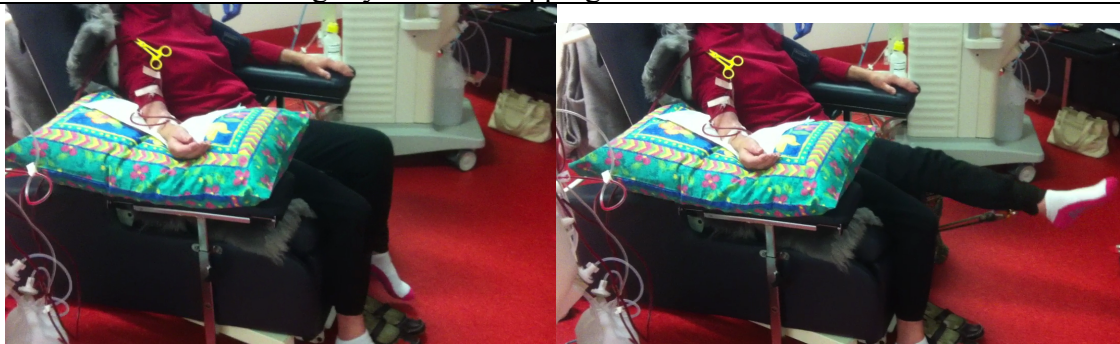
Seated Knee Flexion with machine

This exercise strengthens the muscles at the back of the thighs which brings the lower legs behind the thighs.

1. Sit upright, put both feet on the top leg rest of the machine, shoulder width apart.
2. Elevate the chair so that the legs are rested on the leg rest just behind the ankles.
3. Bend at your knees and bring both feet towards your chair. Then slowly return to original position.

Tips:

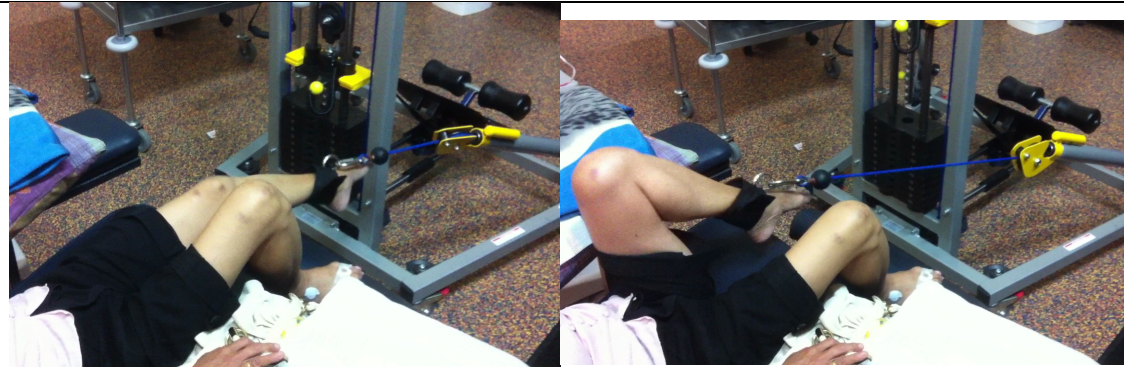
- If the maximum weight available on the machine is too light, use single leg to do the exercise and start with a weight about as heavy as the maximum weight.
- Lean forward slightly to avoid slipping off the chair.



Seated Knee Extension with theraband

This exercise strengthens the muscles at the front of the thighs which straighten the legs.

1. Sit upright, elevate the chair and position the top leg rest just on top of the ankle, legs shoulder width apart.
2. Straighten the legs at the knees with a slow kicking motion against the leg rest. Then slowly return to original position.



Supine bent knee hip flexion with machine

This exercise strengthens the muscles of the lower abdomen that bring the thigh closer to the chest.

1. Secure the exercise machine by locking its wheels, secure the strap to one ankle and lie flat on the back. The exercise cable secured to the ankle should be taut before beginning.
2. Bring the knee towards the chest till it is bent around 90 degree angle.
3. Lower to starting position slowly following the same path. Complete a set before changing to the other leg.

Tips:

- Maintain controlled movements, and keep upper body still during the lift.
- Don't continue lift if back pain occurs.

Appendix 13. Borg Scale for Rating of Perceived Exertion

Rating of Perceived Exertion

“During exercise, we want you to pay close attention to how hard you feel the exercise work rate is. This feeling should reflect your total amount of exertion and fatigue, combining all sensations and feelings of physical stress, effort, and fatigue. Don’t concern yourself with any factor such as leg pain, shortness of breath or exercise intensity, but try to concentrate on your total inner feeling of exertion. Try not to underestimate or overestimate your feelings of exertion; be as accurate as you can.”

(Borg, 1998)

Exertion	RPE
no exertion at all	6
extremely light	7
	8
very light	9
	10
light	11
	12
somewhat hard	13
	14
hard (heavy)	15
	16
very hard	17
	18
extremely hard	19
maximal exertion	20

Reference:

Borg G. Borg's Perceived Exertion and Pain Scales. Human Kinetics. 1998. (Figure 7.3 page 49)

