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Exercise As Adjunctive Therapy In Chronic Kidney Disease

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'If the benefits of exercise could be packaged into a single pill, it would be the single most widely prescribed and beneficial medicine . . .'

R.N. Butler

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List of Abbreviations

AKT	Protein Kinase B
ANOVA	Analysis of Variance
AVF	Arteriovenous Fistula
β_2-M	Beta$_2$-Microglobulin
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CI	Confidence Interval
CSA	Cross sectional Area
CSSD	Continuous Sampling of Spent Dialysate
CT	Computerised Tomography
CV	Coefficient of Variation
CVD	Cardiovascular Disease
DXA	Dual X-Ray Absorptiometery
E3	Ubiquitin ligase
ECG	Echocardiogram
eKt/V$_{urea}$	Equilibrated Kt/V$_{urea}$
FOXO	Forkhead Box Protein of the O Class
GH	Growth Hormone
GFR	Glomerular Filtration Rate
HD	Haemodialysis
HDL-C	High Density Lipoprotein Cholesterol
ICC	Interclass Correlation
IGF- 1	Insulin-like Growth Factor 1

K/DOQI	National Kidney Foundation Disease Outcomes Quality Initiative
KTx	Kidney Transplant
MET	Metabolic Equivalent
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Pathway of Rapamycin
NHS	National Health Service
P	Phosphorylate
PI3K	Phosphoinositide 3 Kinase
PRET	Progressive Resistance Exercise Training
QoL	Quality of Life
RCT	Randomised Controlled Trial
RTx	Renal Transplant
SD	Standard Deviation
SF-36v2	Short Form 36 Version 2
spKt/V_{urea}	Single Pool Kt/V_{urea}
TNF-α	Tumor Necrosis Factor – Alpha
UPS	Ubiquitin Protease System
URR	Urea Reduction Ratio
USRDS	United States Renal Data System

THESIS SUMMARY

Background. Exercise is a natural medicine that has been prescribed for the prevention and management of chronic diseases, to enhance quality of life, improve health status and promote longevity. Current efforts to implement exercise as routine practice in the conventional renal replacement therapy population have been hampered by a lack of randomised controlled data. The aim of this thesis was to investigate the effect of exercise as an adjunctive therapy to enhance outcomes pertaining to renal transplantation, vascular access, haemodialysis adequacy and muscle wasting in Stages four and five Chronic Kidney Disease patients. It was hypothesised that randomised controlled trials employing gold standard outcome measures would reveal significant beneficial effects of exercise that are strongly associated with quality of life, hospitalisation and survival in this patient population.

Reports. The first report presents a systematic literature review of exercise in the kidney transplant population. The largest positive effects were noted on intermediate outcomes such as aerobic fitness and muscle strength. Presumably these adaptations contributed to the trends observed for improvement in quality of life. Whether exercise impacts on outcomes associated with longevity of life requires further study.

The rest of the thesis focused on patients receiving the more popular form of renal replacement therapy, haemodialysis. The first empirical study of the thesis appertaining to vascular access investigated the feasibility of implementing a post-operative forearm exercise intervention for arteriovenous fistula maturation. Exercise had no effect on primary outcomes measures of arterial diameter (95% CI, -0.24 [-1.12; 0.51] mm) and venous diameter (95% CI, 0.16 [-1.84; 1.24] mm). It was concluded that future randomized controlled trials should investigate a similar protocol implemented *before* arteriovenous fistula creation to enhance surgery success and maturation.

The second randomised controlled trial explored the effect of intradialytic exercise in comparison to the traditional prescription of increased dialysis time to enhance dialysis adequacy and solute removal. Increased haemodialysis time, but not exercise, increased equilibrated Kt/V_{urea} compared to control trials (Extra time vs. control: 95% CI, 0.15 [0.05; 0.26]; exercise vs. control: 95% CI, 0.03 [-0.05; 0.12]). Exercise, but not increased time, increased phosphate reduction ratio (exercise vs. control: 95% CI, 8.6 [0.5; 16.7] %; extra time vs. control: 95% CI, 5.0 [-1.0; 11.1] %). Thus intradialytic exercise cannot replace the traditional prescription of increased haemodialysis time, but may be a useful adjunctive therapy for serum phosphate control.

The third study implemented a randomised controlled trial of intradialytic progressive resistance training for muscle wasting. The primary outcome measure of thigh muscle volume, as measured by magnetic resonance imaging, significantly increased following 12 weeks of training compared to a sham exercise control (95% CI, 193 [63; 324] cm^3). Intradialytic resistance exercise elicited an anabolic and strength response in haemodialysis patients. However, a surprising lack of a change in functional capacity despite increased muscle mass warrants further investigation.

Conclusion. The findings suggested that exercise had a beneficial effect on factors relating to outcomes in Stages 4 and 5 Chronic Kidney Disease patients. However, to ensure effectiveness of interventions and to maximize programme efficiency, careful consideration of basic exercise and physiological principles is required. Nevertheless, the observed benefits of exercising outweighed its risks thus supporting the initiative for exercise prescription as an adjunctive therapy for the management of this disease state.

CHAPTER 1

General Introduction

The kidneys are two bean shaped, anatomically complex organs that lie in the retroperitoneal space. They are responsible for several regulatory roles in the body including the maintenance of the body composition with regards to fluid regulation; excretion of metabolic waste products and toxins and the production and secretion of hormones that mediate blood pressure, haematologic and bone health. It is therefore unsurprising that injury, disease or failure of these organs leads to a vast quantity of physiological complications.

Chronic Kidney Disease (CKD) is a progressive an irreversible condition diagnosed by structural or functional abnormalities of the kidneys with a decrease in the filtration function of the nephrons known as the glomerular filtration rate (GFR). The disease progresses through five stages (**Table 1.1.**) with the fifth stage requiring some form of renal replacement therapy such as peritoneal dialysis, haemodialysis or a kidney transplant. Recent reports indicate that 6 – 8.5% of adults in the UK present with CKD. However, Stages 1 and 2 are usually asymptomatic with complications only apparent from Stage 3 (Beddhu, 2009) and as a result an estimated 1.8 million people in the UK are undiagnosed (Kerr *et al.,* 2012). The prevalence of renal replacement therapy has increased by almost 57% over the last decade (Gilg, Castledine & Fogarty, 2012). Although these patients comprise only 2% of the CKD population, more than half of the £1.45 billion NHS CKD cost in England is spent on renal replacement therapy (Kerr *et al.,* 2012).

During stages 1 – 4 clinical approaches aim to slow the progression of CKD. Treatment goals are centred around tight blood pressure control utilizing a multidrug approach as well as lifestyle changes, gylcemic control, management of hyperlipidemia and occasionally protein restriction (Scheippati, Pisoni & Remuzzi 2009). However, when kidney failure occurs in Stage 5, additional therapies are required to address the

complications of water, electrolyte, acid-base, metabolic and organ system disorders. Factors predicting mortality at this stage, such as anaemia, cardiovascular disease, nutritional status, metabolic disorders, dialysis related factors and graft function (Beddhu, 2009) are targeted with an array of therapeutic strategies.

Table 1.1. The National Kidney Foundation Kidney Disease Outcome Quality Initiative classification, diagnosis and action plan for Stages 1- 5 chronic kidney disease (National Kidney Foundation 2002)

Stage	Description	GFR ($ml/min/1.73m^2$)	Clinical Action Plan
1	Kidney damage with normal or increased GFR	>90	Diagnosis treatment; slowing progression; co morbidity risk reduction
2	Kidney damage with a mild decrease in GFR	60 - 89	Estimation of progression
3	Moderate decrease in GFR	30 - 59	Evaluation of treatment complications
4	Severe decrease in GFR	15 - 29	Preparation for renal replacement therapy
5	Kidney failure	< 15	Renal replacement therapy (if uremia is present)

GFR, glomerular filtration rate.

Despite pharmaceutical (Verbeeck & Musuamba, 2009) and technological (Parker, 2000) advancements in renal replacement therapies, in some age groups mortality rates are 30 times higher in Stage 5 CKD patients in comparison to the age matched general population (Castledine *et al.*, 2011). Furthermore, quality of life in this patient population remains poor with patients substantially burdened by a limited physical capacity and dialysis related symptoms (Morsch, Goncalves & Barros, 2006). Efforts to enhance life expectancy and quality of life in this population are therefore required.

Exercise As Medicine in Chronic Kidney Disease.

'If we could give every individual the right amount of nourishment and exercise, not too little, not too much, we would have found the safest way to health.'

Hippocrates (460 – 370 BC).

The principle that physical activity underpins health status predates to ancient Greek medicine and is included in the historical writings of Greek philosophers and physicians. This concept has since been reinstated in the 21st Century. With the population living longer and urbanisation leading to decreased physical activity levels, there has been an increase in chronic diseases. There is irrefutable evidence supporting physical activity status as a risk of chronic disease (Morris & Crawford 1958, Blair *et al.*, 1989, Wei *et al.*, 1999, Barlow *et al.*, 2006, Peel *et al.*, 2009, O'Donnell *et al.*, 2010). Furthermore, in the USA, physical inactivity and poor diet is the second leading actual cause of death following tobacco use (Mokdad *et al.*, 2004). Unsurprisingly there is a wealth of evidence towards implementing exercise for the prevention and management of a wide range of chronic diseases, increasing quality of life and enhancing longevity (Warburton, Nicol & Bredin, 2006).

Physical activity levels in CKD patients are approximately 25% of those recorded in age matched sedentary healthy individuals (Johansen *et al.*, 2000) with one third of patients being unable to carry out activities of daily living unassisted (Ifudu *et al.*, 1994). These patients report very low exercise tolerance with peak oxygen uptakes (VO_{2peak}) of 17 – 20 mL/kg/min (Koufaki, Naish & Mercer, 2001). With oxygen levels of approximately 13 mL/kg/min required to carry out activities of daily living these patients would have to work at 65 -74% of their VO_{2peak} just to carry out their activities of daily living, this clearly having an impact on their functional ability (Ip *et al.*, 2006). These reductions in physical activity are highly correlated with mortality risk (Stack *et al.*, 2005).

Implementing exercise interventions for health benefits in the CKD population, however, may differ from other disease states in that maintenance haemodialysis patients present with what is referred to as 'reverse epidemiology'. This is a phenomenon whereby risk factors of cardiovascular disease in the general population such as obesity, hyperlipidemia and hypertension are seen as protective in maintenance haemodialysis patients and factors such as a low body mass index, reduced serum cholesterol and lower creatinine concentrations are linked with increased morbidity and mortality (Kalantar-Zadeh *et al.*, 2003).

Despite this paradox, over three decades of research has investigated the effects of exercise in the CKD population and suggests that exercise has a myriad of health benefits. According to recent meta-analyses the most established benefits of exercise in the CKD population relate to physical fitness. Increases in maximal oxygen uptake (VO_{2max}) of 17 – 20% have been observed following aerobic and combined aerobic and resistance exercise interventions (Johansen 2008, Segura-Orti & Johansen, 2010).The mechanisms behind these increases are not yet completely understood. However, they could be due peripheral to adaptations such as the increase in muscle capillary density observed following aerobic exercise (Sakkas *et al.*, 2003b) or central adaptations such as increased ejection fractions and stroke volumes observed at rest and during exercise following aerobic exercise in this patient cohort (Deligiannis *et al.*, 1999). Yet despite these increases, cardiorespiratory fitness levels of trained haemodialysis patients still lie below the normative values of the age matched general population (Segura-Orti & Johansen, 2010) suggesting there are limitations to exercise capacity. As the criteria for VO_{2max} is rarely achieved in this patient population, often due to lower limb fatigue, these limitations are thought to be at the peripheral rather than the central level (Kouidi, 2001). With regards to oxygen carrying capacity, it could be thought that anaemia associated with chronic kidney disease (Wish, 2009) could be such a limiting factor.

However, although increases in cardiorespiratory fitness have been observed with complete correction of anaemia through erythropoietin therapy (Macdougall *et al.*, 1990), fitness levels still remain 38% below age matched healthy controls (Barany *et al.*, 1993) as well as below population normative values (Macdougall *et al.*, 1990, Barany *et al.*, 1993). Therefore, limitations may lie elsewhere in the oxidative transport chain, possibly in the form of blunted aerobic enzyme activity (Sakkas *et al.*, 2003b) for example. Furthermore, limitations could potentially lie at the skeletal muscle (Diesel *et al.*, 1990) with myopathies commonly observed in this disease state (Diesel *et al.*, 1993, Moore *et al.*, 1993).

In addition, exercise has been shown to increase strength and physical function in this patient population (Segura-Orti & Johansen, 2010; Johansen, 2007; Heiwe & Jacobson, 2011). As increases in isokinetic strength have been found to be a better predictor of exercise capacity as compared to oxygen carrying capacity in haemodialysis patients (Diesel *et al.*, 1990), it is no surprise that with increases in VO_{2max}, strength gains have been also been observed. The mechanisms behind increases in physical function and the extent that exercise capacity influences physical function is yet to be established. A possible mechanism may be through the changes in lean body composition following exercise (Heiwe & Jacobson, 2011); indeed such changes have previously been associated with habitual physical activity (Johansen *et al.*, 2000).

Further benefits of exercise in CKD patients, although less established, include cardiovascular adaptations (Cheema, 2008) including changes in blood pressure, resulting in reductions in antihypertensive medications (Miller *et al.*, 2002; Macdonald *et al.*, 2005), reductions in systemic inflammation (Cheema, 2008), improved weight control in obese patients (Segura-Orti & Johansen, 2010) and increased health related quality of life (Heiwe & Jacobson, 2011).

Despite these reports exercise has failed to be established as part of routine care in CKD. This is due in part to the fact that the generalisation of these findings is compromised as there appears to be a lack of randomised controlled trials (RCT) with few outcomes being examined in more than one RCT (Segura-Orti & Johansen 2010, Heiwe & Jacobson, 2011). Furthermore, most studies present small sample sizes due to recruitment difficulty in this cohort (Segura-Orti & Johansen, 2010). In addition, many studies have failed to address issues concerning the practicalities of implementing exercise interventions in this population. Finally, interventions have often failed to follow basic exercise and physiological principles to ensure effectives and efficiency of exercise programmes.

This thesis aimed to add randomised controlled data to the growing evidence of the benefits of exercise as an adjunctive therapy in patients with Stages 4 & 5 CKD. Factors relating to survival were explored in detail. The first of these was renal transplantation, the treatment of choice for Stage 5 CKD patients. The second factor was dialysis access, an essential aspect of renal replacement therapy which is usually implemented in Stage 4 CKD in preparation for haemodialysis (Fluck & Kumwenda, 2011). The third factor, dialysis adequacy, was a central aspect in patient management as patients move from Stage 4 to Stage 5 CKD and haemodialysis commences. The final factor was muscle wasting, an established problem in patients who are in Stage 5 and have been receiving maintenance haemodialysis.

Renal Transplantation

Kidney transplantation is a form of renal replacement therapy whereby an organ transplant from a deceased or living donor is received by a patient with 5 CKD. Patients who receive a transplant often present with a greater quality of live and experience increased longevity in comparison to those awaiting a transplant (Mannon, 2009; MacPhee *et al.*, 2012). It is therefore unsurprising that renal transplantation is the preferred method of renal replacement therapy. Yet despite advances in surgical and immunosuppressive strategies (Casesa, 2007) survival and aspects of quality of life such as physical functioning still remain below age matched sedentary healthy population (MacPhee *et al.*, 2012; Painter, 1997). Furthermore, a high percentage of transplant recipients present with co-morbidities such as cardiovascular disease, hypertension, new-onset diabetes after transplantation, obesity, haemotoligic complications, metabolic disorders and bone diseases (Mannon, 2009). Interventions aimed at further enhancing quality of life and survival as well as managing post transplantation outcomes and com-morbidities are therefore warranted .

Vascular Access for Haemodialysis

Vascular access, the point where blood leaves and is returned to the body during extracorporeal treatment, is a fundamental requirement for haemodialysis. Vascular access is the single most important cause of morbidity in the haemodialysis population and accounts for 20% of hospitalisations (Roy-Chaudhury *et al.,* 2005). Types of vascular access include permanent or temporary tunneled catheters, arteriovenous grafts or arteriovenous fistulae (AVF). Current recommendations suggest an AVF as a the gold standard type of access (National Kidney Foundation, 1997) as they require fewer interventions (Perera *et al.,* 2004), result in fewer infections (Nassar & Ayus, 2001) and have lower hospitalisation rates (Dhingra *et al.,* 2001) compared to other forms of access. In the UK, chances of survival after 6 months of dialysis initiation are increased by 20% by dialysing via an AVF in comparison to a tunnelled catheter (Fluck, 2011).

An AVF is a surgically formed anastamosis of an artery and a vein (**Figure 1.1.**), predominantly created in the arm. When the AVF is created, shear stress elicits vascular remodeling via nitric oxide mediated vasodilatation as a result of the chronic nine fold increase in blood flow immediately after surgery (Konner, Nonnast-Daniel & Ritz, 2003; Wedgwood, Wiggins & Guillou, 1984). The resultant increases in vein diameters, allowing easier cannulation and higher blood flows through the AVF, have been associated with greater dialysis adequacies (Chan *et al.,* 2008).

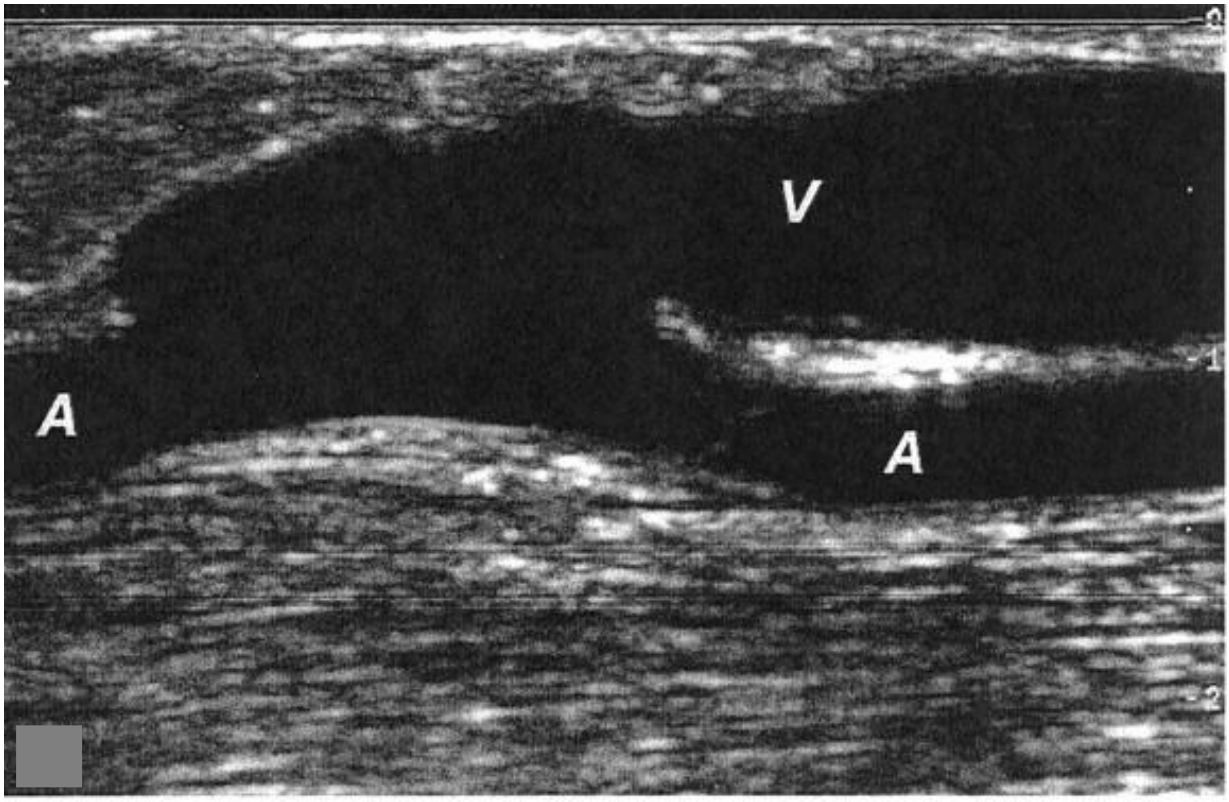

Figure 1.1. A longitudinal, B mode ultrasound view, of a radiocephalic arteriovenous fistula created by anastomosing the cephalic vein to the radial artery at the wrist in a side to end fashion (Konner, Nonnast-Daniel & Ritz 2003). A; radial artery; V, cephalic vein.

Despite recommendations in favour of AVF placement, only 40% of haemodialysis patients commence dialysis with an AVF and only 41% of patients are dialysing via this type of access three months after initiating dialysis (Fluck 2011). These figures fail to reach British Renal Association standards recommending 85% of prevalent haemodialysis patients dialyse via an AVF (Fluck, Kumwenda 2011). This is probably due to the fact that more than half of fistulae created fail to mature adequately for the use of haemodialysis (Wong *et al.*, 2011). Several factors have been linked with fistulae failure including neointimal hyperplasia, accessory or 'branching' veins (Beathard *et al.*, 2003; Feldman *et al.*, 2003), surgical technique (Feldman *et al.*, 2003) and co-morbidities such as vascular disease and heart failure (Ravani *et al.*, 2005). However, the main biological reason for fistula failure appears to be insufficient

increases in vascular dilation and blood flow (Asif, Roy-Chaudhury & Beathard, 2006). Interventions aimed at decreasing fistula failure, possibly through increasing post operative vascular dilation and blood flow are warranted. Furthermore, as dialysis access plays such a large role in morbidity and mortality, care should be taken to avoid secondary AVF failure.

Haemodialysis Adequacy and Solute Removal

When the kidney fails, biochemically active waste products known as uremic toxins accumulate and contribute to uremic syndrome. One method of removing such toxins is the extracorporeal form of renal replacement therapy known as haemodialysis administered in Stage 5 CKD. The efficacy of removing uremic toxins by haemodialysis is known as 'dialysis adequacy' and is based on the rate of solute diffusion from the blood across the dialyzer membrane.

Dialysis adequacy is currently measured by the clearance of the 'small' molecule urea (National Kidney Foundation, 2006). Urea clearance can be quantified by calculation of Kt/V_{urea} defined as the urea clearance over dialysis time proportional to total body water, or by urea reduction ratio (URR), defined as the fractional reduction in blood urea nitrogen during a single haemodialysis session expressed as a percentage. The clearance of urea has been chosen as a marker for adequate solute removal for several reasons. Firstly, its blood concentration is increased in uremia and therefore its removal should hypothetically indicate decreased uremia. Secondly, it is of low molecular weight allowing easy transfer across the dialysis membrane as well as a rapid compartmental diffusion. When referring to urea kinetics, this allows the implementation of a single pool model representation of total body water for most applications.

It stands well documented that urea clearance is a significant predictor of hospitalisation (Hakim *et al.,* 1994; Maiorca *et al.,* 1995) and mortality (Desai *et al.,* 2009). Patients who have a low urea clearance, dialysing at a Kt/V_{urea} <1.0 (Maiorca *et al.*, 1995) or a URR <60% (Owen *et al.,* 1993) have a significantly increased relative risk of death. The likelihood of survival increases with enhanced urea clearance with mortality risk decreasing by 7% with every 0.1 increment in Kt/V_{urea} (Held *et al.,* 1996) until an optimum Kt/V_{urea} of 1.3 is reached (Iseki, Tozawa & Takishita, 2003; Marshall

et al., 2006). There appears to be a "ceiling effect" with survival benefits reaching a plateau at a Kt/V_{urea} of 1.3 (Held *et al.,* 1996; Charra *et al.,* 1992) to 1.6 (Charra *et al.,* 1992). In fact patients dialysing at a particularly high Kt/V_{urea} or URR (above 71%) actually show an increased relative risk of mortality (Chertow *et al.,* 1999; Salahudeen, Dykes & May, 2003). This could be due to "over dialysis" depleting electrolytes which could lead to the onset of potentially fatal arrhythmias or, more likely, the harmful effect of vigorous dialysis on malnourished patients (Chertow *et al.,* 1999; Salahudeen, Dykes & May, 2003). The urea clearance and mortality relationship, therefore, appears to be one of a reverse J shaped nature (Chertow *et al.,* 1999).

It should be noted that the use of small molecule clearance as the only indicator of adequate dialysis remains controversial. It could be argued that urea, previously defined as a 'mild' toxin (Bergstrom & Furst, 1986), does not represent the kinetic behaviour of more toxic water-based solutes such as phosphate and xanthine for example (Vanholder & Glorieux, 2003), or that of other uremic toxins that are protein bound or have a higher molecular weight (Dhondt *et al.,* 2000). Middle molecules and protein bound solutes have toxic effects which may relate to inflammation, cardiovascular disease and mortality (Vanholder *et al.,* 2003) in CKD patients. It cannot be denied that these solutes play a role in uremic syndrome and investigation of urea and creatinine alone may represent an over-simplified view of dialysis adequacy (Vanholder, Van Laecke & Glorieux, 2008).

$Beta_2$-Microglobulin (β_2-M) is produced in the majority of cells as an expression of the human leukocyte antigen class 1, and has long been used as a marker of uremic toxin "middle molecules" and dialysis adequacy. Normative serum values of this molecule lie between 1.5 and 3 mg/L. In CKD patients, however, levels usually range from 20 – 50 mg/L and have been reported up to 100 mg/L in extreme cases (Drueke & Massy, 2009). Efficient removal of β_2-M is imperative as high serum concentrations of

this molecule have been associated with mortality. Okuno *et al.,* (2009) revealed β_2-M to be a significant, independent predictor of mortality with serum levels $\geq$ 32.2 mg/L resulting in a significantly higher death rate. In support of this, Cheung *et al.,* (2006) reported an increased relative risk of mortality of 1.11 for every 10 mg/L increase in serum β_2-M level with serum levels of 42.5 mg/L providing a 60% greater risk of death compared to levels $\leq$ 27.5 mg/L (Cheung *et al.,* 2006). In particular, β_2-M is associated with infectious, rather than cardiovascular deaths, with a 21% increase in the relative risk of an infectious death with every 10mg/L increase in serum concentrations (Cheung *et al.,* 2006, Cheung *et al.,* 2008). Reasons for this decrease in survival may be that β_2-M is representative of other middle molecule toxins with similar kinetics. Furthermore, the accumulation of this molecule is a precursor to the development of β_2-M amyloidosis, a disorder where amyloid fibrils invade synovial membranes and osteoarticular sites, causing destructive osteoarthropathies (Drueke & Massy, 2009).

Middle molecule removal, such as β_2-M clearance is enhanced with the use of high flux dialysis membranes. However, results of the 'Hemodialysis (HEMO) study' reported that the use of such membranes had no significant impact on all cause mortality or hospitalisation compared to low flux membranes (Cheung *et al.,* 2003). Yet reduced serum levels of β_2-M decrease the risk of all cause mortality and dialyser clearance has been shown to be a predictor of serum β_2-M (Cheung *et al.,* 2006). Tentatively speaking, the use of high flux membranes alone may not result in large enough improvements in β_2-M clearances to cause clinically significant changes in serum concentrations. Therefore adjunctive strategies to enhance β_2-M clearance are warranted.

Phosphate has previously been realised as a marker of inorganic substances. Phosphate retention is an additional consequence of renal failure, contributing to secondary hyperparathyroidism which ultimately results in bone diseases and further

uremic complications. Serum phosphate levels in CKD are considerably elevated ranging from 6.2 – 6.3 mg/dL compared to normative values ranging from 2.6 – 4.5 mg/dL (Pohlmeier & Vienken, 2001). High serum phosphate levels are noteworthy as they have been associated with a higher risk of mortality. Patients presenting with serum phosphate levels above 6.5 mg/dL have a 27% greater relative risk of mortality compared to those with serum levels between 2.4 – 6.5 mg/dL (Block *et al.,* 1998). Although the underlying mechanisms through which hyperphosphatemia increases mortality remain indistinct, associations with cardiovascular risk factors such as haemodynamic disturbances and soft tissue cardiovascular calcification appear to relate increased serum phosphate levels with cardiovascular death (Qunibi, 2004). Despite concerted efforts of nephrologists to lower serum phosphate levels only 55% of haemodialysis patients in the UK obtain target values of this inorganic solute (Dawnay *et al.,* 2010). **Table 1.2.** lists the current interventions implemented to reduce serum phosphate levels and their associated difficulties. Evidently there is a requirement for treatments to normalize serum phosphate levels in haemodialysis patients.

Table 1.2. Current interventions to prevent hyperphosphatemia in haemodialysis patients (Pohlmeier, Vienken 2001, Gutzwiller *et al.,* 2003).

Intervention	Limitation
Dietary restriction of phosphate intake	-Restricts adequate protein intake
Phosphate binders to absorb phosphate in the gut	-Side effects such as aluminium intoxication, hypocalcaemia, gastrointestinal problems
Higher clearance through more changes in dialysis	-Increased dialysis blood flow resulting in higher Kt/V fails to increase phosphate removal -Decreased removal following 1 hour due to limited transport from the intracellular space
Increased treatment time Increased treatment frequency	-Organisational problems -Cost implications -Patient unwillingness -Impractical
Correcting acidosis through bicarbonate therapy	-Discontinuity in data

Previous efforts to enhance dialysis treatment have centred around factors such as increasing dialysis dose, through manipulation of dialysis time and dialyser flows, and enhancing larger molecule clearance by utilizing dialyzer membranes with higher porosity or flux. These interventions were addressed in the randomised controlled HEMO study (Eknoyan *et al.,* 2002) whereby the effects of a standard or high dose of haemodialysis and the use of low or high flux membranes on all cause mortality were investigated. The surprising results of this study revealed that the risk of all cause mortality was not significantly influenced by dialysis dose or membrane flux. More frequent dialysis sessions have also been suggested. However, this concept is confronted with the barriers of patient compliance and cost implications (Locatelli *et al.,* 2005). A major challenge for dialysis therapy, therefore, is to improve the efficiency of dialysis with interventions aimed at enhancing more than just urea clearance alone being highly warranted. Strategies aimed at achieving clinical standards of dialysis adequacy

as well as reducing dialysis time and thus impacting on patient QoL and financial costs, are sought after.

Muscle Wasting in Maintenance Haemodialysis Patients

Muscle wasting is known as a debilitating response to disuse and disease resulting from a disturbance in the normal balance between protein synthesis and breakdown. Muscle atrophy is frequently observed in maintenance haemodialysis (HD) patients (Workeneh & Mitch, 2010) and has been reported via several methods of body composition analysis. Cross sectional histological studies elicit significant type IIa and IIx muscle fibre atrophy, portrayed by a reduced fibre cross sectional area, in CKD patients compared to healthy controls (Sakkas *et al.*, 2003). In addition diminished lean body mass, measured by dual energy x-ray absoptiometry, has previously been reported in this patient population (Heimburger *et al.*, 2000; Macdonald *et al.*, 2004). Additionally, magnetic resonance imaging (MRI) scans reveal less contractile tissue in the lower leg in CKD patients compared to healthy sedentary controls (Johansen *et al.*, 2003) confirming muscle atrophy.

The main causes of muscle wasting in CKD (**Figure 1.2.**) have been identified as anorexia, malnutrition and vitamin D deficiency (Bossola *et al.*, 2006; Mak *et al.*, 2011); co morbid conditions such as chronic heart failure, insulin resistance, excess angiotensin II and ageing (Workeneh & Mitch, 2010; Franssen, Wouters & Schols, 2002); inflammation and hormone resistance (Iglesias *et al.*, 2004); severe acidosis (Mak *et al.*, 2011; Rajan & Mitch, 2008); increased resting energy expenditure (Utaka *et al.*, 2005); the actual HD process itself (Lim, Yarasheski & Flanigan, 1998) and diminished physical function leading to disuse atrophy (Johansen *et al.*, 2003).

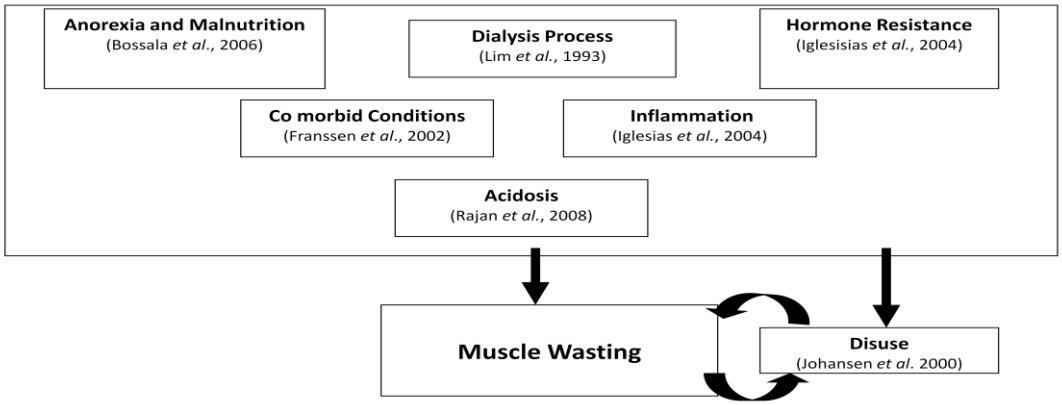

Figure 1.2. Factors contributing to muscle wasting in CKD patients. Johansen *et al.,* (2000) suggested that these factors may lead to inactivity which leads to further muscle wasting augmenting a vicious cycle of disuse atrophy.

Figure 1.3. summarises the hormonal physiological mechanisms behind protein synthesis and breakdown. In CKD hormone irregularities prevent phosphoinositite 3-kinase (pI3K) activity thereby lowering protein kinase B (AKT) activation. This results in a decrease in serine kinase protein activation ultimately leading to a decrease in protein synthesis via the mammalian target of rapamycin pathway (mTOR). Furthermore, reduced AKT activation results in insufficient energy to phosphorylate class O forkhead box proteins (FOXO), allowing them to enter the cell nucleus and up regulate ubiquitin lipase (E3) production thereby activating the ubiquituin protease system (UPS) which promotes protein degradation. In cases of inflammation tumor necrosis factor –alpha (TNF-α) has also been found to unregulate E3 lipases activation the UPS system as well as activating the Capase 3 system. Suppression of AKT has also been linked to activation of the Capase 3 system (Rajan, Mitch 2008, Mak, Cheung & Roberts 2008, Mak *et al.,* 2011).

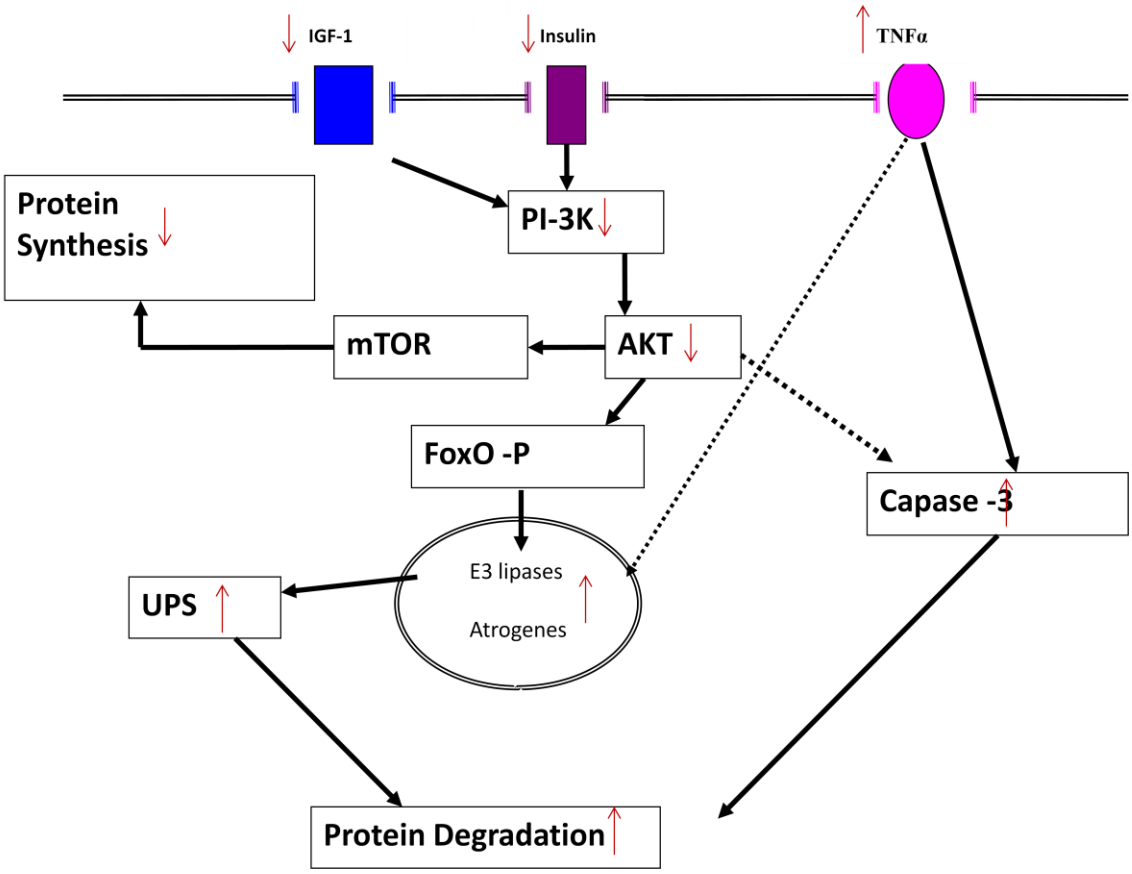

Figure 1.3. Simplified schematic representation of hormonal mechanistic physiology of protein synthesis and breakdown. Adapted from (Rajan, Mitch 2008). Red arrows highlight changes prevalent in CKD patients. AKT, protein kinase B; E3, ubiquitin lipase; FOXO, forkehead box class O; FOXO – P; phosphorylated forkehead box class O; IGF -1, insulin growth factor; mTOR, mammalian target of rapamycin; TNF –α; tumor necrosis factor-alpha; UPS, ubiquitin protease system.

Catabolism of muscle protein in the CKD population poses as a major problem for several reasons. Firstly, a positive correlation between muscle mass and mortality has previously been reported (Huang *et al.*, 2010) with decreases in lean body mass actually showing to be an independent predictor of mortality (Desmeules *et al.*, 2004). There could be several explanations for this relationship. The oxidation of essential amino acids in the muscle resulting in protein catabolism could result in a failure to produce immunoproteins that protect against injury and infection (Richards, 1980). Furthermore, it could be that factors causing protein energy wasting provide non traditional risk

factors to cardiovascular disease (CVD) thus further increasing the mortality risk of patients CKD (Bonanni *et al.,* 2011). A further consequence of muscle wasting is an increased risk of hospitalisation as total muscle mass has been reported to be inversely correlated the number of hospitalisation days (Bajardi *et al.,* 1991). Additionally, as previously mentioned, wasting is associated with factors such as insulin resistance, inflammation and oxidative stress which all pose as risk factors to co morbid conditions such as diabetes and CVD (Bonanni *et al.,* 2011; Lee *et al.,* 2007).

Further consequences of muscle wasting in this cohort include a reduced reduced quality of Life (QoL) as well as reduced physical function. Muscle wasting could indirectly affect QoL through its relationship with physical function as physical functioning has been found to affect QoL above social and emotional functioning (Churchill *et al.,* 1987). As mentioned previously haemodialysis patients report physical function levels below age norms (Painter *et al.,* 2000). This may be a result of muscle wasting as medium to strong positive correlations have been revealed between muscle quantity, functional capacity and strength in HD patients (Macdonald *et al.,* 2004;Johansen *et al.,* 2003). Atrophy has also been shown to be associated with reduced oxygen extraction at the muscle (Marrades *et al.,* 1996). Further consequences are noted as reduced physical activity has a detrimental effect on muscle morphology, muscular strength and motor control (Clark, 2009; Clark, Fernhall & Ploutz-Snyder, 2006) thus creating an augmentative vicious cycle between physical function and muscle wasting (**Figure 1.2.**).

Previous successful anabolic interventions have included the use of androgens, growth hormone (Storer, 2009), anabolic steroids (Johansen *et al.,* 2007; Macdonald *et al.,* 2007) and nutritional supplementation (Storer, 2009) . However, not only are longer term studies required for the safety and efficacy of these interventions (Storer, 2009) but in some cases an increase in muscle mass has not had the expected beneficial effect on

physical function (Johansen *et al.*, 2007; Macdonald *et al.*, 2007). Interventions to reverse muscle wasting and enhance physical function in CKD patients are therefore warranted.

Thesis Aims

The aim of this thesis was to investigate the effect of exercise as an adjunctive therapy in Stage four and five CKD patients, providing a variety of developmental opportunities to the PhD candidate. The first report of the thesis aimed to explore the benefits of exercise in kidney transplant patients via a systematic review of existing literature. The empirical aspect of the thesis investigated the effect of exercise in enhancing outcomes pertaining to vascular access, haemodialysis adequacy and muscle wasting. It was hypothesised that randomized controlled trials employing gold standard outcome measures would reveal significant beneficial effects of exercise on outcomes that are strongly associated with quality of life, hospitalisation and survival in this patient population (Roy-Chaudhury *et al.,* 2005; Desai *et al.,* 2009; Desmeules *et al.,* 2004). It should be highlighted, however, that hospitalisation and survival *per se* were not investigated in the reported trials.

Thesis Layout

The thesis is presented in a 'paper style' format in that the information presented in each chapter is reported in the scientific style required for publication in peer reviewed journals.

Chapter 2 reports a systematic review on the effects of physical activity on immediate outcomes in kidney transplant patients. The paper has been published in *Advances in Chronic Kidney Disease* 2009, Vol. 16, No. 6.

Chapters 3 address issues pertaining to vascular access in Stage 4 and 5 CKD patients, exploring the effects of an eight week progressive resistance forearm exercise intervention on AVF maturation. A feasibility study for the implementation of a large multicentre trial is reported. This paper will be submitted for peer review to *Nephrology, Dialysis, Transplantation*.

Chapter 4 addresses dialysis adequacy in Stage 5 maintenance haemodialysis patients and investigates the acute effects of exercise carried out during dialysis on dialysis adequacy and solute removal. This study will be submitted for peer review to *The American Journal of Kidney Disease*.

Chapter 5 addresses muscle wasting in Stage 5 maintenance haemodialysis patients, exploring the implementation of a 12 week intradialytic progressive resistance training for anabolism in maintenance haemodialysis patients. This study has been submitted for peer review to *Medicine and Science in Sports and Exercise*.

Funding sources are disclosed at the beginning of each chapter. The editorial contributions of Dr Jamie Macdonald are acknowledged.

CHAPTER 2

Kidney transplantation: A systematic review of interventional and observational studies of physical activity on intermediate outcomes.

Abstract

Background. Kidney transplant patients have decreased quality and longevity of life. Whether exercise can positively affect associated outcomes such as physical functioning, metabolic syndrome, kidney function, and immune function, has only been addressed in relatively small studies. Thus the aim of this systematic review was to determine effects of physical activity level on these intermediate outcomes in kidney transplant patients.

Methods. We electronically and hand searched to identify 21 studies (six retrospective assessments of habitual physical activity and 15 intervention studies including six controlled trials). After study quality assessment, intermediate outcomes associated with quality and longevity of life were expressed as correlations or percentage changes, plus effect sizes.

Results. Habitual physical activity level was positively associated with quality of life and aerobic fitness, and negatively associated with body fat (medium to large effect sizes). Exercise interventions also showed medium to large positive effects on aerobic capacity (10 to 114% increase) and muscle strength (10 to 22% increase). However, exercise programmes had minimal or contradictory effects on metabolic syndrome, and immune and kidney function.

Conclusions. In kidney transplant patients, physical activity intervention is warranted to enhance physical functioning. Whether exercise impacts on outcomes associated with longevity of life requires further study.

Introduction

The number of patients with chronic kidney disease receiving a kidney transplant is increasing, with 18,000 transplants completed annually in the USA alone (USRDS, 2008). With better immunosupression regimes and antibiotics, acute cases of morbidity and mortality following transplantation have been substantially reduced. Nevertheless, outcome (poor quality of life, morbidity and mortality) of kidney transplant patients (KTx) remains poor compared to the general population .

As a consequence of improving longevity of life, *quality* of life is now of critical importance to the transplant patient. Quality of life is made up of various domains including physical functioning (Kouidi, 2004). Disappointingly, studies have shown that physical functioning after transplantation remains only marginally improved compared to when on haemodialysis (Nyberg *et al.,* 1995)and fails to normalize to even that of the sedentary healthy population (Painter *et al.,* 1997). In KTx both decreased aerobic capacity and muscle strength, due to use of immunosuppressive medications and also a persistent sedentary lifestyle, are likely to contribute to the reduced physical functioning typically observed (Dew *et al.,* 1997). Cardiovascular fitness is also a strong independent predictor of survival (Sietsema *et al.,* 2004).

Comorbid conditions are also of increasing importance to the transplant patient, affecting both quality and longevity of life. Many comorbid conditions present in KTx have similar antecedents as in the general population. For example, cardiovascular disease, the biggest cause of death in transplant patients, is similarly associated with components of the metabolic syndrome (USRDS, 2008). Also of specific importance to the kidney recipient is graft survival. Many modifiable risk factors of late graft failure exist. Fat mass gain is typical post transplantation (van den Ham, Kooman & van Hooff, 2002), and obesity has been associated with poor graft outcome (Jindal &

Zawada, 2004). Additionally, as in all patients with chronic kidney disease, inadequate control of hypertension and hyperglycemia are likely to quicken loss of kidney function (Briggs, 2005).

Consequently care of the kidney transplant patient must now aim to improve quality of life, reduce chronic medical complications and prevent graft failure. The Surgeon General states that exercise can increase physical functioning and improve quality of life. Additionally exercise is advocated for prevention and treatment of hypertension, hyperlipidemia, diabetes, and cardiovascular disease in both healthy persons and in chronic kidney disease patients receiving maintenance haemodialysis (Cheema & Singh, 2005).

Potential efficacy of physical activity in KTx is suggested by the annual Transplant Games, where very motivated patients have been shown to achieve near normal levels of physical fitness (Painter *et al.,* 1997). Unfortunately confirmation is lacking of similar efficacy in the general kidney transplant population. However a number of smaller observational and experimental studies investigating physical activity have been completed. Although there may be insufficient data to determine direct effects of exercise on quality of life, morbidity, mortality and graft failure, combining results from smaller studies may provide useful information on efficacy of exercise for intermediate outcomes such as physical functioning, cardiovascular disease risk factors, diabetes, immune function, bone disease and kidney function. Thus the aim of this systematic review is to determine effects of physical activity on these outcomes in KTx.

Methods

The following databases were searched: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), the Physiotherapy Evidence Database (PEDro) and Sports Discuss using key words relating to the disease condition (e.g. kidney) and to the intervention (e.g. physical activity). Hand searching was also used but grey matter such as technical reports were ignored. Included studies were case studies, retrospective or prospective designs, with participants aged > 18 yrs and a functioning graft. Selected studies investigated physical activity as an independent variable and detailed outcomes of quality of life, physical functioning, cardiovascular disease risk factors, immune function, diabetes, bone disease or kidney function. Studies on joint kidney pancreas transplants were excluded.

Study quality was assessed subjectively. For studies on habitual physical activity, quality of determination of exercise participation was assessed: A (accelerometer, metabolic cart or doubly labeled water), B (prospective diary or pedometer) and C (retrospective questionnaire). For interventional studies, scores were instead based on quality of training protocols compromising: i) specificity to measured outcomes, ii) sufficient overload to have an effect and iii) progression to maintain overload. Each factor was given a score of 1 (none/not known), 2 (inadequate) or 3 (adequate) and an overall study composite score from C (inadequate) to A (adequate) was calculated. For all studies risk of bias was determined compromising: i) selection bias ii) performance bias iii) attrition bias and iv) detection bias. Again, each factor was given a score of 1 (high risk/not known), 2 (medium risk) or 3 (low risk) and an overall composite score from C (high risk) to A (low risk) was given.

Relevant information (see column heads on **Tables 2.2. – 2.4.**) was displayed in summary tables. Simple correlational data was summarized as Pearson's *r* values;

effect sizes were interpreted directly from *r* as small (0.1), medium (0.3) or large (0.5) (11). Multiple regression data was summarized as R^2 values; effect size was calculated as $R^2 / (1 - R^2)$ and interpreted as small (0.02), medium (0.15) or large (0.35) (Cohen 1992). Between group comparisons were expressed as % differences and within group comparisons were expressed as % change from baseline; effect size was then calculated as $(x_1 - x_2) / SD_2$, and interpreted as small (0.2), medium (0.5) or large (0.8) (Cohen 1992). For cohort intervention studies with non-comparable control groups (**Table 2.3.**), data for the KTx exercise group only were treated as a within group comparison. For experimental studies with comparable control groups (**Table 2.4.**), within group comparisons were expressed as % change from baseline for both groups; interaction effect size was calculated as recommended by Bausell and Li (2002) (effect size $difference_1$ – effect size $difference_2$) / 2 and were interpreted as small (0.1), medium (0.3) or large (0.5).

Results

Included study designs. Twenty-one studies (plus eleven case studies detailed in supplementary material) were identified that met inclusion criteria (**Figure 2.1.**). Of the included studies, six were retrospective assessments of habitual physical activity level on outcome (including one longitudinal study) (**Table 2.2.**); nine were time series designs with outcomes obtained pre and post an exercise intervention and had either no control group (five studies) or a non comparable control group such as healthy persons or alternative diseases (four studies) (**Table 2.3.**); and six studies were comparably controlled trials (included four randomized controlled trials) (**Table 2.4.**). Subgroups of KTx studied included glucose intolerant or not (Orazio *et al.,* 2011; Sharif, Moore & Baboolal, 2008), metabolic syndrome or not (Armstrong *et al.,* 2006), and physically active or not (Painter *et al.,* 1997). Control groups (**Table 2.4.**) were generally normal routine care, with no sham exercise or attention control groups, except for one study that compared exercise to a statin (Gonzalez-Molina *et al.,* 1993). One study also included the untrained contralateral leg as a control (Horber *et al.,* 1987).

Excluded studies. Two studies were excluded due to repetition of results from other studies (Painter *et al.,* 2001; Horber *et al.,* 1985a; Horber *et al.,* 1985b); two studies were excluded because of lack of any outcome data (Svoboda, 2001; Joy, Neyhart & Dooley, 2000); one study was excluded because of investigation of acute effects only (Cosio-Lima *et al.,* 2006); and one study was excluded because it could not be obtained (Leasure *et al.,* 1999).

Case studies. Ten relevant case studies were identified (Einollahi *et al.,* 2008, Mourning, 2006; Howard-Jones, 2005; Browne *et al.,* 2001; Grafstein, Fernandes & Boldt, 1997; Hestin *et al.,* 1993; Roney & Wellington 1985; Bradlow *et al.,* 1984; Fanti *et al.,* 2002). Three studies were personal accounts of RTx patients advocating benefits

of exercise (Mourning, 2006; Howard-Jones, 2005; O'Moore, 1999). One study was of an RTx patient who participated in boxing without identifiable acute damage to the kidney (Einollahi *et al.*, 2008). Two studies identified injuries to the kidney (subcapsular bleeding) following heavy lifting of boxes and impact by a squash ball (Browne *et al.*, 2001; Roney & Wellington, 1985). Some studies identified Achilles tendon rupture but these were not caused by participation in exercise programmes so are not reviewed in detail here. One study noted exercise induced steal of kidney blood flow following transplant with the renal artery connected to the left external iliac artery, and later femorofemoral bypass (Fanti *et al.*, 2002). A number of non-peer reviewed case studies highlighted athletes competing at professional level in the sport (data not shown).

Study quality. Study quality is provided in detail in supplementary material. All cross sectional studies relied upon retrospective self report questionnaire assessments of physical activity level, and were thus all graded C (poor) (**Table 2.1.**). In seven of the 15 intervention studies (Sharif, Moore & Baboolal 2008; You *et al.*, 2008; Juskowa *et al.*, 2006; Korabiewska *et al.*, 2007; Triolo *et al.*, 1989; Surgit *et al.*, 2001; Gonazales-Morino *et al.*, 1993), physical activity interventions were of poor quality and did not adhere to (or did not report data on) the basic principles of exercise training. In contrast three (Kempeneers *et al.*, 1990; van den Ham *et al.*, 2007; Miller *et al.*, 1987) and five studies (Horber *et al.*, 1987; Horber *et al.*, 1985a; Violan *et al.*, 2002; Painter *et al.*, 2003; Painter, Krasnoff 2002) obtained scores of B (medium) and A (excellent), respectively.

However no studies obtained maximum scores for control of bias and thus results must be interpreted accordingly.

Subject demographics. Five hundred and eighty five subjects (496 KTx, 52 other transplants, 16 haemodialysis patients, 21 healthy controls) were included in studies of

habitual physical activity (**Table 2.2.**), whilst 340 subjects (281 KTx, 4 other transplants, 25 haemodialysis patients, 30 healthy controls) were included in interventional studies with non comparable control groups (**Table 2.3.**) and 398 KTx subjects were included in interventional studies with comparable control groups (**Table 2.4.**). Reported age ranged from 27 ± 4 years to 56 ± 12 years. Time with transplant ranged from two days to 109 ± 52 months (~nine years), while dialysis vintage pre-transplant, when reported, ranged from 3 ± 2 to 54 ± 45 months. Co-morbidity data was often not reported, but exclusion criteria in the majority of studies detailed contraindications to exercise testing including cardiovascular disease, and four studies excluded diabetics (Korabiewska *et al.,* 2007; van den Ham *et al.,* 2007; van den Ham *et al.,* 2005; van den Ham *et al.,* 2000).

***Exercise interventions*.** Exercise interventions were run as outpatient supervised programmes in four studies (Horber *et al.,* 1987; Horber *et al.,* 1985a; Juskowa *et al.,* 2006; van den Ham *et al.,* 2007; Violan *et al.,* 2002); as inpatient programmes where sessions were alternately supervised or unsupervised in one study (Juskowa *et al.,* 2006); were started as supervised programmes then progressed to at home unsupervised in two studies (Korabiewska *et al.,* 2007; Miller *et al.,* 1987); or were home based in three studies (Sharif, Moore & Baboolal, 2008; Painter *et al.,* 2003; Painter *et al.,* 2002) (**Tables 2.3. & 2.4.**). Two studies did not mention the exercise setting (Kempeneers *et al.,* 1990; Gonzalez-Molina *et al.,*1993). Reported mode of exercise in intervention studies included aerobic (typically walking, jogging, cycling or swimming) in seven studies (Sharif, Moore & Baboolal, 2008; Surgit *et al.,* 2001; Miller *et al.,* 1987; Violan *et al.,* 2002; Painter *et al.,* 2003; Painter *et al.,* 2002, Gonzalez-Molina *et al.,* 1993), aerobic and strength training in one study(Kempeneers *et al.,* 1990), isokinetic training in two studies (Horber *et al.,* 1987; Horber *et al.,* 1985a), alternative interventions such as calisthenics, ball games and a DanJeon breathing exercise programme in two

studies(You *et al.*, 2008; Kempeneers *et al.*, 1990), or a combination of strength training and alternative interventions (e.g. isometric activities) in two studies (Juskowa *et al.*, 2006; Korabiewska *et al.*, 2007). Duration of programmes ranged from one month (Juskowa *et al.*, 2006) to ~ two years (Miller *et al.*, 1987); frequency ranged from one (Sharif, Moore & Baboolal, 2008) to seven sessions per week (Juskowa *et al.*, 2006, Korabiewska *et al.*, 2007) (typically two to three per week). Intensity of aerobic training, when reported, was typically 60 – 80% of heart rate or peak power max (Kempeneers *et al.*, 1990; van den Ham *et al.*, 2007; Violan *et al.*, 2002; Painter *et al.*, 2003; Painter *et al.*, 2002), except for one study completed at 40 – 60% max heart rate (Miller *et al.*, 1987). Progressive resistance training was of low to moderate intensity, progressing to 3 x 10 repetitions at 60% of one repetition maximum (strength) and 3 x 30 repetitions at 35% of one repetition max (strength/endurance) (van den Ham *et al.*, 2007). When used, isokinetic training was completed at maximal effort (Horber *et al.*, 1987; Horber *et al.*, 1985a). Eight studies failed to report sufficient detail regarding exercise prescription (Sharif, Moore & Baboolal, 2008; You *et al.*, 2008; Juskowa *et al.*, 2006; Korabiewska *et al.*, 2007; Surgit *et al.*, 2001; Miller *et al.*, 1987; Violan *et al.*, 2002; Gonzalez *et al.*, 1993).

Participant compliance. Ten of the fifteen exercise intervention studies did not report data on compliance. Of the investigations that did report compliance, one study using a supervised outpatient programme suggested attendance at 75% of organized sessions over six months (Kempeneers *et al.*, 1990), while others using home based exercise suggested 67% (Painter *et al.*, 2002; Painter, 2008) to 88% (Sharif, Moore & Baboolal, 2008) of subjects were partaking in regular exercise at ~12 months. Another home based study suggested 38% were fully compliant, 54% partially compliant, and 2% non compliant to a six month intervention including both dietary restriction and exercise intervention (Triolo *et al.*, 1989).

Quality of life. Self reported measures of quality of life were reported in one study of habitual physical activity level (Painter *et al.,* 1997) (**Table 2.2**). The cross sectional data reported significantly greater scores for physical functioning (large effect size) and role limitation due to physical health domains (small effect size) in active compared to inactive organ transplant patients (Painter *et al.,* 1997). Only one of two intervention studies (**Table 2.4.**) revealed significant increases in quality of life in exercising patients as compared to controls (You *et al.,* 2008); this study was of poor quality and effect size was unknown. The other study (of better quality) showed only trends for improvement in physical functioning components ($p = 0.06$, small interaction effect sizes) (Painter *et al.,* 2002).

Physical functioning. Muscle strength was assessed in seven studies (Horber *et al.,* 1987; Horber *et al.,* 1985a; You *et al.,* 2008; Korabiewska *et al.,* 2007; Kempeneers *et al.,* 1990; van den Ham *et al.,* 2007; Painter *et al.,* 2003). Habitual physical activity level did not independently influence muscle strength (van den Ham *et al.,* 2007) (**Table 2.2.**). However, all exercise interventions significantly increased both upper and lower body strength, and effect sizes were generally medium to large, especially in studies with focused strengthening exercises (e.g. calisthenics (Kempeneers *et al.,* 1990) or isokinetic training (Horber *et al.,* 1987; Horber *et al.,* 1985a) (**Table 2.3.**). In comparably controlled studies interaction effect sizes were small but differences in strength gain between groups remained significant (**Table 2.4.**).

Cross sectional data revealed that habitual physical activity accounts for 17 to 34% of the variance in VO_{2peak} (medium effect size, **Table 2.2.**), and more active individuals had ~40% increased aerobic capacity (large effect size). Seven of seven interventional studies reported significant increases in exercise capacity following an exercise intervention (**Table 2.3. & 2.4.**). Increase in VO_{2peak} ranged from 10% to 29%, while increases in maximal metabolic equivalents (MET) ranged from 19% to 114%.

Effect sizes ranged from small to large in non-comparably controlled studies (**Table 2.3.**) and were medium in comparably controlled studies (**Table 2.4.**).

***Components of Metabolic Syndrome*.** The number of people who were physically active was higher in those without compared to those with metabolic syndrome (Armstrong *et al.,* 2006). Specifically, blood pressure was measured in three interventional studies (Kempeneers *et al.,* 1990; Miller *et al.,* 1987; Painter *et al.,* 2003) but exercise showed no significant effects on this outcome (**Table 2.3. & 2.4.**). Additionally one study measured hypertensive medication use (Painter *et al.,* 2002) (also reported in Painter *et al.,* 2003) but this outcome also failed to be responsive to exercise (**Table 2.4.**). Although one cross sectional study (Orazio *et al.,* 2011) suggested substantially higher exercise participation in patients who were glucose tolerant compared to those who were intolerant, interventional studies (Sharif, Moore & Baboolal, 2008; Juskowa *et al.,* 2006) revealed disparate findings on blood glucose levels and the only comparably controlled study suggested a small effect size (Juskowa *et al.,* 2006). Six studies included blood lipid measures ; Gonzalez-Molina *et al.,* 1993), and exercise intervention paradoxically caused both increases and decreases of these measures. Medication use for diabetes and blood lipid control was either not reported or did not change in the above studies.

Body Composition. Cross sectional studies revealed that habitual physical activity accounts for 10 to 21% of variance in body fat measures (Orazio *et al.,* 2011; van den Ham *et al.,* 2000), and that body fat was lower in more active individuals (Painter *et al.,* 1997) (medium effect size). However intervention studies were less successful in reducing body fat (Painter *et al.,* 2003; Painter *et al.,* 2002) (very small to small effect sizes). In contrast, habitual physical activity had no (van den Ham *et al.,* 2005) or even negative (van den Ham *et al.,* 2000) effects on lean body mass (**Table 2.2.**) but intervention studies showed significant positive effects of exercise programmes on

parameters related to muscle (Horber *et al.,* 1987; Horber *et al.,* 1985). Still, not all studies concurred that intervention increased muscle (Painter & Krasnoff, 2002), and effect sizes were small. Habitual physical activity level had only small effects on bone related parameters (Grotz *et al.,* 1995)(**Table 2.2.**) but an interventional study using impact exercise showed a large positive effect on bone turnover markers (Kempeneers *et al.,* 1990) (**Table 2.3.**).

Immune function. Two studies investigated markers of immune function in RTx. The first (Surgit *et al.,* 2001) showed positive effects of exercise on various immune parameters without inducing rejection of the graft (**Table 3.3.**). The second (Juskowa *et al.,* 2006) showed a non significant increase (medium effect size) of an immune associated pro-inflammatory cytokine (interleukin 18) (**Table 4.4.**).

Kidney function. No studies measured effects on graft failure. However five studies assessed estimated glomerular filtration rate or serum creatinine levels (Sharif, Moore & Baboolal, 2008; You *et al.,* 2008; Juskowa *et al.,* 2006; Korabiewska *et al.,* 2007; Miller *et al.,* 1987; Painter *et al.,* 2002) (**Tables 2.3. & 2.4.**). One study of poor quality (You *et al.,* 2008) showed significant positive effects of exercise on kidney function (effect size unknown, **Table 2.4.**). Three studies showed non-significant and only very small or small effects of exercise (Sharif, Moore & Baboolal, 2008; Korabiewska *et al.,* 2007; Painter & Krasnoff, 2002; Painter *et al.,* 2002). In one uncontrolled study (Miller *et al.,* 1987) serum creatinine increased during the intervention period (statistically non-significant but medium effect size, **Table 3.3.**).

Adverse events. Adverse events were generally poorly reported. However, adverse events were specifically mentioned in Kempeeners *et al.* (1990) who carried out an alternative exercise intervention involving calisthenics, aerobic exercises and ball games. Injuries occurred in 3 out of 16 participants and were reported as medial tibial

stress syndrome, stress fracture and acute musculotendinous injury. In contrast, Violan *et al*. (2002) reported "no noteworthy sports related injuries after training".

Discussion

Observational studies. Identified studies assessing habitual physical activity level and outcomes all relied on self-report retrospective questionnaires, rather than more objective assessments of physical activity or energy expenditure. Only one study utilized a longitudinal design (Grotz *et al.,* 1995), with others relying on a cross sectional design. Nevertheless, surprisingly strong relationships were identified in these studies between physical activity level and outcomes (Orazio *et al.,* 2011; Sharif, Moore & Baboolal, 2008; Armstrong *et al.,* 2006; Korabiewska *et al.,* 2007; Painter *et al.,* 2002), with physical activity level explaining 10 – 34% of variance in exercise capacity and body composition. Furthermore, substantially lower exercise participation was noted in those with glucose intolerance, metabolic syndrome and obesity compared to those without these conditions (Painter *et al.,* 1997; Orazio *et al.,* 2011; Sharif, Moore & Baboolal, 2008; Armstrong *et al.,* 2006). Conversely, in a study investigating activity level as the independent variable (i.e. highly active versus sedentary participants), aerobic capacity and quality of life was higher in the active group (Painter *et al.,* 1997). Of course whether physical activity is a cause or consequence of these conditions is not determined from these data. Furthermore, some studies also showed minimal effects of physical activity on certain outcomes: habitual physical activity had, for example, minimal effects on bone (Grotz *et al.,* 1995) and muscle related parameters (van den Ham *et al.,* 2005; van den Ham *et al.,* 2000). These lack of effects may be due to crude measures of activity level, as more specific measures of habitual activity showed different findings dependent on whether occupational, sport or leisure activity was assessed (van den Ham *et al.,* 2000).

Interventional studies. The interventional studies located and reviewed herein provide further support for benefits of exercise on certain outcomes in KTx patients.

However, results must be interpreted cautiously. To date, relatively few studies have been completed in this population, and only six controlled trials were identified, compared to 20 in the hemodialysis population (Cheema & Singh, 2005). Furthermore, quality of the interventions was occasionally poor. Intervention studies utilized exercise programmes that often did not meet general training principles, with half of the studies scoring the lowest grade of C. In these studies, specificity, overload and progression were not ensured, even when accounting for application to a chronically diseased population. For example, it is generally believed that low exercise capacity in KTx is primarily due to physiological alterations at the peripheral level (van den Ham *et al.,* 2005). Of the studies with aerobic capacity as an outcome, only one study has included the most anabolic of exercise interventions, progressive resistance training (van den Ham *et al.,* 2007), while other studies utilized purely aerobic interventions (Sharif, Moore & Baboolal, 2008; Surgit *et al.,* 2001; Miller *et al.,* 1987; Painter & Krasnoff, 2002; Gonzalez-Molina et al 1993) or nonspecific "strengthening" exercises (Sharif, Moore & Baboolal, 2008; You *et al.,* 2008; Juskowa *et al.,* 2006; Korabiewska *et al.,* 2007; Surgit *et al.,* 2001). Furthermore sufficient overload was not achieved (or not reported) in some studies (Korabiewska *et al.,*2007; Juskowa *et al.,* 2006; Sharif, Moore & Baboolal, 2008;You *et al.,* 2008; Surgit *et al.,*2001}} Gonzalez et al 1993), perhaps because of fear of injuring patients, or due to financial and practical constraints of implementing programmes of sufficient duration supervised by exercise professionals (Gordon *et al.,* 2005). It is therefore somewhat surprising that despite ignoring these training principles, the reviewed studies show some remarkable results on reported outcomes, as discussed below. Presumably the low physical functioning of the population (Dew *et al.,* 1997) means that even inefficient interventions can have beneficial effects.

Quality of life. This review suggests that quality of life intermediates such as the physical functioning components of strength (Horber *et al.,* 1987; You *et al.,* 2008; Juskowa *et al.,* 2006; Korabiewska *et al.,* 2007; Kempeneers *et al.,* 1990; van den Ham *et al.,* 2007) and aerobic capacity (Surgit *et al.,* 2001; Kempeneers *et al.,* 1990; Miller *et al.,* 1987; Violan *et al.,* 2002; Painter & Krasnoff,2002; Painter, 2008) seem undoubtedly improved in KTx with exercise intervention. However, whilst quality of life was improved in those with higher habitual physical activity (Painter *et al.,* 1997), increased physical functioning did not translate into significant improvements in self reported quality of life in all intervention studies (Painter & Krasnoff, 2002; Painter *et al.,* 2002). This small effect may be due to the unusually physically active control participants recruited in centers that implement exercise interventions. Due to the perceived importance of quality of life to the now longer living kidney transplant patient, and the lack of return to normal values of quality of life with transplantation (Dew *et al.,* 1997), these findings require urgent confirmation.

Longevity of life. No studies have investigated end points of morbidity, mortality, or graft failure, but intermediate outcomes of survival and specifically of cardiovascular, diabetic and bone disease have been investigated. As stated, all exercise interventions improved aerobic capacity, which has been linked with survival in chronic kidney disease (Sietsema *et al.,* 2004). The improvements were substantial (10-114%) and as expected were greatest in studies of longer duration. The optimal mode for increasing aerobic capacity is not discernible from these few studies due to differences in study duration, but it is notable that comparable improvements were obtainable in home based unsupervised studies *et al.,* 2002; Painter *et al.,* 2002) as in outpatient, supervised studies (Surgit *et al.,* 2001; Kempeneers *et al.,* 1990; van den Ham *et al.,* 2007;Violan *et al.,* 2002)

In contrast, effects of exercise on the metabolic syndrome were minimal in the KTx studies reviewed. Positive effects of exercise on total cholesterol were confined to poor quality studies (Sharif, Moore & Baboolal, 2008; You *et al.*, 2008) and otherwise were minimal, with small effect sizes (Juskowa *et al.*, 2006; Painter *et al.*, 2003). This is a response similar to that seen in non-diseased populations over similar durations (< one year) (Roberts & Barnard, 2005). Generally, high density lipoprotein (HDL-C) is more responsive to exercise intervention (Roberts & Barnard, 2005). While some studies reviewed herein suggest improved HDL-C with training, their results must be interpreted with caution as bias in these studies was likely (Triolo *et al.*, 1989) Gonzalez-Molina *et al.*, 1993). In a better quality study, Painter showed small positive effects on HDL-C (Painter *et al.*, 2003). In explanation, although the utilized exercise programme was of sufficient duration and intensity to elicit more favorable lipid changes in non-CKD persons, it failed to show any reduction in body fat (Painter *et al.*, 2002), a primary factor associated with lipid profiles. Blood lipid responses to exercise may also be attenuated in this population due to increased dietary intake following transplantation, and confounding effects of corticosteroids on body fat (van den Ham, Kooman & van Hooff, 2002).

Similarly, exercise failed to elicit expected changes in blood pressure or hypertensive medications. Diastolic and systolic blood pressure is typically lowered by 7.4 and 5.8 mmHg, respectively, with exercise intervention in otherwise healthy persons, and responds regardless of exercise mode (Roberts & Barnard, 2005). Thus the lack of response in the three studies herein (Kempeneers *et al.*, 1990; Miller *et al.*, 1987; Painter *et al.*, 2003) is surprising. However, two studies were uncontrolled and may have been confounded by natural progression of hypertension customary to KTx (Briggs, 2005), and only one study measured medication dose (which did not reduce) (Painter *et al.*, 2002).

Data on glycaemic control is similarly difficult to interpret. One study completed specifically in patients selected as glucose intolerant suggested substantially lowered (large effect size) fasting blood glucose following combined exercise and dietary intervention (Sharif, Moore & Baboolal, 2008), whilst a second controlled study without concomitant dietary intervention showed minimal effect (Juskowa *et al.*, 2006). Both studies were at high risk of bias and should be interpreted cautiously.

The final component of metabolic syndrome is body fat. Surprisingly only one group has specifically measured body fat as an outcome (Painter *et al.*, 2003; Painter *et al.*, 2002), and exercise had minimal effect (small effect size) over the period of one year. Other parameters of body composition that are linked to outcome in the CKD population include muscle mass (Kato *et al.*, 2003). When this outcome was assessed as lean body mass or muscle cross sectional area, exercise effects were very small to small (Horber *et al.*, 1987; Horber *et al.*, 1985a; van den Ham *et al.*, 2007; Painter *et al.*, 2002) with specific interventions aimed at targeting muscle size and function, such as isokinetic training, unsurprisingly showing more significant benefits. In studies with very small effects, training was unspecific (e.g. aerobic (Painter *et al.*, 2002)), or overload may not have been achieved (van den Ham *et al.*, 2007). Interestingly this later study (van den Ham *et al.*, 2007) also showed increased lean body mass in a healthy control group prescribed the same exercise programme, suggestive of anabolic resistance in the RTx group (Kato *et al.*, 2003). An uncontrolled study also showed substantial benefits (large effect sizes) of exercise on bone turnover (Kempeneers *et al.*, 1990), suggestive of bone formation with potential benefits for reducing fracture risk and improving associated outcome. Although data is scarce, effects on body composition seemed to occur even in patients on corticosteroids (Kempeneers *et al.*, 1990; van den Ham *et al.*, 2007), although the response may be slightly attenuated (Horber *et al.*, 1987).

Infection remains a significant cause of death in RTx patients (USRDS, 2008)and chronic moderate exercise may be beneficial to prevent infectious illnesses in normal persons (Mackinnon, 2000). Still, the task of preserving immune function to prevent infection whilst avoiding graft rejection is delicate. The scant data reviewed herein suggests positive effects on various immune parameters. However as no study has measured the actual incidence of infections and too few subjects have been studied to completely determine consequences for graft rejection, the significance of these findings remain unclear.

Graft function. Components of metabolic syndrome have been implicated in progression of kidney failure. As little effect of exercise was noted on metabolic syndrome, it is unsurprising that exercise also showed little benefit on kidney function (estimated glomerular filtration rate or serum creatinine) in the studies with this outcome measure (Sharif, Moore & Baboolal, 2008; Miller *et al.*, 1987; Painter *et al.*, 2002; Gonzalez-Molina *et al.*, 1993). Although positive effects were noted in some studies (You *et al.*, 2008; Korabiewska *et al.*, 2007), high risks of bias including unmatched kidney function (Korabiewska *et al.*, 2007) at baseline may have confounded these results.

Safety. Adverse events were poorly reported in most studies. When mentioned, all injuries were musculoskeletal, often associated with participation in non-recommended competitive and high impact sports, and resolved successfully. Exercise was not associated with any cardiac events. Whilst data is scarce, and most studies excluded participants contraindicated for exercise testing (reducing generalisability), these exercise risks seem similar to that noted for the general CKD population (Cheema & Singh, 2005). Furthermore specific issues highlighted as risks for exercising KTx (Griffin, 1998) were not realized (or not reported) in the studies reviewed.

Implications for practice. With the current evidence base it is impossible to state which modes of exercise are most efficient and to state the minimum dose required, but most studies completed to date have utilized aerobic exercise (60 – 80% of heart rate or peak power maximum) with consequent benefits for aerobic capacity. However, as discussed above, theoretically weight training may be more specific to requirements of the transplant patient (van den Ham *et al.,* 2005). Other than non-specific "strengthening" programmes, weight training has only been used in one study at relatively low intensities (60% of 1 repetition max), and isokinetic training, whilst effective, requires expensive equipment. Thus progressive resistance training interventions are encouraged, but must start at low intensities with adequate progression to ensure safety but sufficient overload. Alternatively calisthenics and ball games may be particularly effective for strength and bone parameters. But in general, exercise prescriptions could be based on guidelines as provided for specific conditions such as hypertension, hyperlipidemia, diabetes, and bone disease, as appropriate to the individual goals and comorbidities of the individual patient.

Importantly none of the studies reviewed have specifically addressed different methods to encourage exercise participation. A perceived facilitator to physical activity is "encouragement from healthcare providers" (Sanchez *et al.,* 2007) and hopefully the evidence base reviewed herein may increase confidence of care teams to recommend exercise participation. Note that unsupervised at home programmes seem effective, with associated reductions in cost of implementation as compared to supervised inpatient programmes. However, the importance of regular follow up to aid compliance, following exercise training principles, and intervening for a minimum of six months, must be emphasized. The included studies also relied on scientific measures (such as VO_{2peak}) for exercise prescription and outcome assessment. Yet healthcare teams could utilize simpler measures such as ratings of perceived exertion

(Borg, 1982) to monitor exercise intensity and the Senior Fitness Test (Rikli & Jones, 2001) to assess outcomes.

Review limitations. This review is limited by a lack of grey literature searching. Publication bias may thus affect results. Due to the small number of published studies, this review necessarily relied on cross sectional and uncontrolled intervention studies, and meta-analytical methods were not possible for the few and diverse outcomes currently reported. Of particular concern is the general improvement in outcomes that occur spontaneously following transplantation, which may confound uncontrolled observational studies. However, most of the included uncontrolled studies had mean transplant vintages of more than one year, partially reducing this effect. Even when combining studies, many questions remain underpowered for their reported outcomes, and results should be interpreted accordingly. Finally, biased study designs may confound findings of positive benefits of exercise. Conversely, some of the studies utilised poor interventions that may explain lack of effects.

Future research. Future studies must thus utilize designs and dissemination methods that meet Consort statement standards. Particular attention must be paid to avoiding bias. When selecting participants, age of participants may affect response in this population. Researchers must decide whether to make results generalisable to the RTx population, for example by including diabetics, or whether to have strict inclusion criteria to simplify result interpretation. If quality of life is an outcome measure, attention control arms are encouraged to reduce performance bias. Care must be taken to avoid confounding by steroid dose, anemia improvement, and RTx vintage. Attrition must be dealt with *a priori*, with compliance and adverse events recorded and detailed. Finally, blinding of assessors and use of *intention to treat* designs are needed to avoid detection bias.

Summary. In the general population physical activity has a myriad of potential benefits and positively affects outcome. No studies have directly assessed effects of exercise on end points such as morbidity/mortality and graft failure in RTx patients. However, positive effects were noted on intermediate outcomes such as aerobic fitness and muscle strength. Presumably these adaptations contributed to the trends observed for improvement in quality of life. However, in the few and relatively small studies reviewed, exercise had no consistent effect on metabolic syndrome or kidney function. Future studies must use better quality interventions and study designs to enable more detailed evaluation of these outcomes.

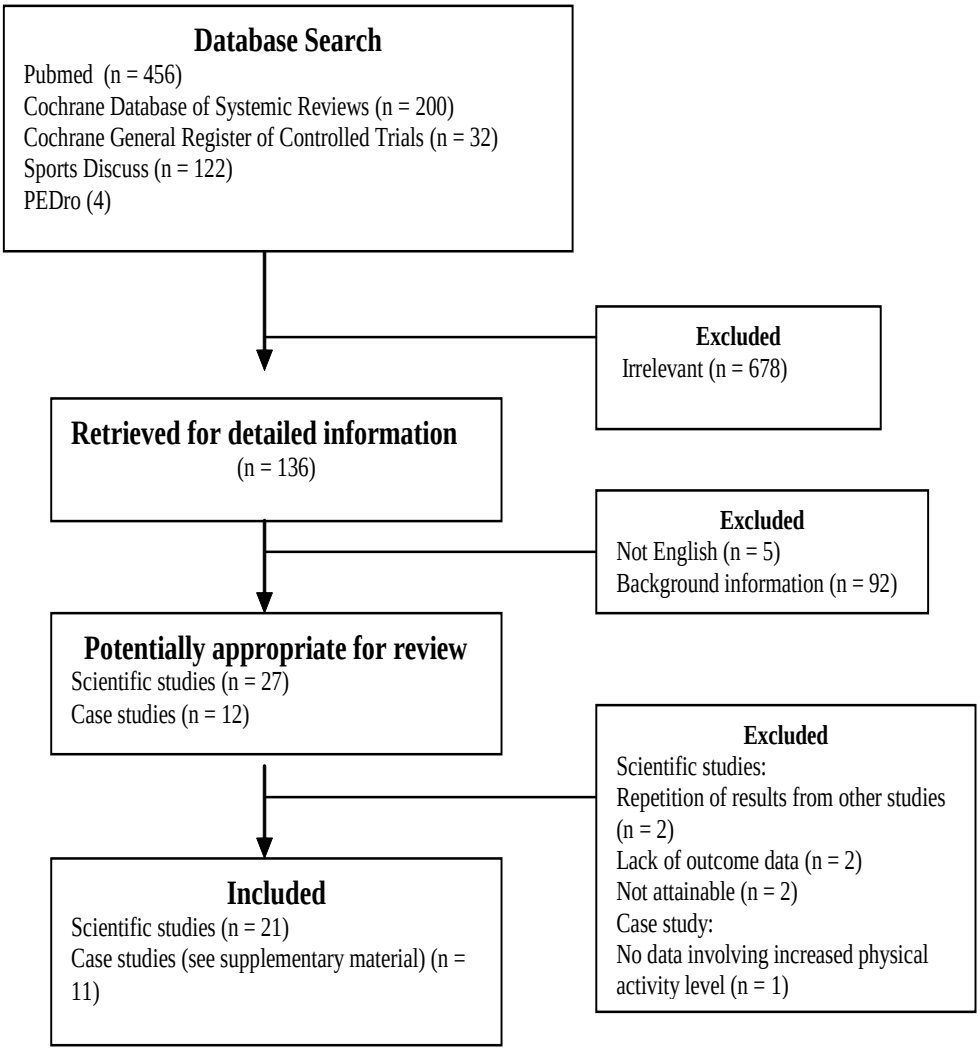

Figure 2.1. Flow diagram of selection of studies to review.

Table 2.1. Quality assessment of reviewed studies.

Studies of habitual physical activity	**Habitual physical activity assessment method**			**Bias**				
Author			**Overall quality**	Selection bias	Performance bias	Attrition bias	Detection bias	**Overall bias risk**
Orazio, (2009)			**C**	2	1.5	1	1	**C**
Armstrong, (2006)			**C**	1	1.5	2	2	**B/C**
van den Ham, (2005)			**C**	2	3	3	1	**B**
van den Ham, (2000)			**C**	2	3	2	1	**B**
Painter, (1997)			**C**	1	3	2	1	**B**
Grotz, (1995)			**C**	2	1	1	1	**C**

Exercise intervention studies (without a comparable control group)	**Exercise intervention training principles**				**Bias**				
Author	Specificity	Overload	Progression	**Overall quality**	Selection bias	Performance bias	Attrition bias	Detection bias	**Overall bias risk**
Sharif, (2008)	2	1	1	**C**	1	1	2	1	**C**
van den Ham, (2007)	2.5	2	2	**B**	2	2	2	1	**B**
Violan, (2002)	3	3	2	**A**	1	2	1	1	**C**
Surgit, (2001)	2	1	1	**C**	1	2	1	1	**C**
Kempeneers, (1990)	2	2	2	**B**	1.5	2	2	1	**B/C**
Horber, (1987)	3	2	3	**A**	2	2	1	1	**C**
Miller, (1987)	2	2	2	**B**	2	1	2	1	**C**

Horber, (1985)	3	2	3	**A**	1	2	1	1	**C**
Triolo, (1989)	1	1	1	**C**	2	1	1	1	**C**

Exercise intervention studies (with a comparable control group)		**Exercise intervention training principles**					**Bias**			
Author	Specificity	Overload	Progression	**Overall quality**	Selection bias		Performance bias	Attrition bias	Detection bias	**Overall bias risk**
					Concealed allocation	Random assignment / success				
You, (2008)	1	1	1	**C**	1	No	1	1	1	**C**
Korabiewska, (2007)	2	1	1	**C**	1	No	2	1	1	**C**
Juskowa, (2006)	1	1	1	**C**	1	Yes / 1	2	1	1	**C**
Painter, (2003)	3	3	3	**A**	3	Yes / 3	2	1	1	**B**
Painter, (2002)	2	3	3	**A**	3	Yes / 3	2	2.5	1	**A/B**
Gonzalez, (1993)	1	1	1	**C**	1	Yes / 2	2	1	1	**B/C**

Study Quality: A, adequate; C, inadequate; 1, none/not known; 2, inadequate; 3, adequate. Study Bias: A, low risk; B, moderate risk; C, high risk; 1, high risk/not known; 2, medium risk; 3, low risk

Table 2.2. Effects of habitual physical activity on outcomes in kidney transplant patients.

Author	Design	Groups	Transplant vintage (months)	Questionnaire	Outcome	Differences between groups or correlation	Effect size
Orazio (2009)	2 group cross sectional	Glucose Intolerant (n = 47) Glucose Tolerant (n = 35)	55	Physical Activity Statewide Questionnaire	**Diabetes**: Habitual physical activity in glucose tolerant vs. glucose intolerant	127 % †	?
					Habitual physical activity on glucose intolerance by multiple regression (multivariate odds ratio)	0.940 †	?
					Body comp: Habitual physical activity on % body fat by multiple regression (R^2)	0.211 †	0.27 M
Armstrong (2006)	2 group cross sectional	Metabolic syndrome (n = 45) No metabolic syndrome (n = 26)	81.6	-Physical Activity Statewide Questionnaire	**Exercise capacity**: Habitual physical activity on VO_2 max by multiple regression (R^2)	0.17 †	0.20 M
					Metabolic syndrome: Number of physically active in without metabolic syndrome vs. with metabolic syndrome	67 % †	?
van den Ham (2005)	3 group cross sectional	KTx (n = 35) Haemodialysis (n = 16) Healthy control (n = 21)	84	Baecke Questionnaire	**Exercise capacity**: Habitual physical activity on VO_2 max by multiple regression (R^2)	0.342 †	0.52 L
					Body composition: Habitual physical activity on lean body mass by multiple regression (R^2)	? ns	?
					Muscle strength: Habitual physical activity on quadriceps peak torque by multiple regression (R^2)	? ns	?
van den Ham (2000)	1 group cross sectional	KTx (n = 77)	109	Baecke Questionnaire	**Body composition**: Occupational activity index & lean body mass by correlation (r)	-0.348	0.35 M
					Occupational activity index & fat mass, % fat, %	? ns	?

					lean body mass by correlation (*r*)		
					Leisure activity index & body mass index by correlation (*r*)	- 0.310 †	0.31 M
					Leisure activity index & fat mass by correlation (*r*)	-0.288 †	0.29 M
					Leisure activity index & lean body mass, % lean body mass, & % body fat by correlation (*r*)	? ns	?
					Sport activity index & body mass index, fat mass, lean body mass & % body fat by correlation (*r*)	? ns	?
Painter (1997)	2 group cross sectional	Active (*n* = 98) Control (*n* = 30) (Of which KTx (*n* = 76) Other transplants (*n* = 52))	97	"Self report"	**Body composition**: Body mass index: active vs. control	- 10% †	0.59 M
					% body fat: active vs. control	- 19% †	0.55 M
					Exercise capacity: VO_2 peak: active vs. control [included other transplant types]	+ 35% †	0.95 L
					VO_2 peak: active vs. control [KTx only]	+ 47% ?	?
					Quality of Life: physical functioning: active vs. control	+ 15% †	0.81 L
					Role physical: active vs. control	+ 23% †	0.44 S
Grotz (1995)	1 group 12 month observation	KTx (*n* = 155)	55	"Standard" questionnaire	**Bone**: Energy expenditure during sports & bone gain by correlation (*r*)	0.2 †	0.20 S
					Habitual physical activity & vitamin D therapy on bone gain by multiple regression (R^2)	? ns ($p = 0.07$)	?

†, significant result whereby $p \leq 0.05$; ?, information not provided in paper; S, small; M, medium; L, large.

Table 2.3. Effect of exercise interventions on outcomes in kidney transplant patients (studies without a comparable control group).

Author	Design	Groups	Transplant vintage (months)	Exercise prescription	Outcome	Differences vs. baseline in KTx exercise group[significance of within group main effect]	Effect size
Sharif, 2008	2 group intervention	Glucose intolerant + exercise (*n* = 36) Glucose tolerant + no exercise (*n* = 79)	6 (minimum)	[A]Unsupervised [B]Home based [C]Aerobic (walking, jogging & swimming) [D]? [E]120 min [F]1 x week [G]6-12 months	**Diabetes**: 2 hr postprandial blood glucose **Kidney function**: Estimated glomerular filtration rate **Lipids**: Total cholesterol	- 15 % ‡ - 2 % ns - 7 % ns	0.76 L 0.07 vS 0.27 S
van den Ham, 2007	3 group intervention	KTx (*n* = 35) Haemodialysis (*n* = 16) Healthy control (*n* = 21)	86	[A]Supervised [B]? [C]Aerobic (cycling, walking, swimming, gymnastics) & strength (progressive resistance training) [D]70% of peak watts 3 x 10 reps @ 60% max 3 x30 @ 35% max [E]120 min [F]2 x per week [G]3 months	**Exercise capacity**: VO^2 peak **Strength**: Quadriceps peak torque **Body composition**: Lean body mass (male) Lean body mass (female)	+ 10 % ‡ + 10 % ‡ + 0 % ns - 2 % ns	0.36 S 0.29 S 0.02 vS 0.12 vS

Violan, 2002	2 group intervention	KTx (n = 12) Haemodialysis (n = 9)	74	[A]Supervised [B]? [C]Aerobic (walking, jogging, ball games) [D]60% max HR (progresses) [E]50 min [F]3 x week [G]6 months	**Exercise capacity**: VO_2 peak	+ 18 % ‡	?
Surgit, 2001	1 group intervention	KTx = 12 Liver transplant = 4	12 - 24	[A]Supervised [B]? [C]Aerobic (cycling) [D]? [E]45 min [F]3 x week [G]2 months	**Exercise capacity**: VO_2 peak **Immune function**: T helper cells CD4+ to CD8+ ratio IgG & IgM levels Natural killer cells IgA T & B lymphocytes, activated T lymphocytes	+ 11 % ‡ + ? % ‡ + ? % ‡ + ? % ? + ? % ‡ ? ? ? ? ? ?	? ? ? ? ? ? ?
Kempeneers, 1990	1 group intervention	KTx (n=24) [detailed n=16]	63	[A]Supervised [B]? [C]Calisthenics, aerobic, ball games [D]Max 80% max HR [E]60 mins [F]3 x per week [G]6 months	**Blood pressure**: Systolic blood pressure Diastolic blood pressure **Exercise capacity**: VO_2 peak **Strength**: Quadriceps peak torque **Bone:** Serum calcium Serum alkaline phosphate activity Serum inorganic phosphate Urine hydroxyprolie excretion	- 2 % ns - 3 % ns + 29 % ‡ + 22 % ‡ + 1 % ns + 90 %‡ + 0 % ns - 50 % ‡	0.12 vS 0.24 S 1.36 L 1.19 L 0.26 S 1.09 L 0.00 vS 1.03 L

Author	Design	Groups	Transplant vintage (months)	Exercise prescription	Outcome	Differences vs. baseline in KTx exercise group	Effect size
Triolo 1989	Controlled trial	Low protein diet (*n* = 26) Control (*n* = 26) [Both groups exercise]	?	[A]Supervised & unsupervised [B]Oupatient & home based [C]? [D]? [E]? [F]? [G]6 months	**Lipids**: Total cholesterol [control group data] High density lipoprotein cholesterol [control group data]	+ 21 % ‡ + 49 % ‡	0.71 M 1.39 L
Horber, 1987	2 groups intervention	KTx (*n* = 9) Healthy control (*n* = 9)	60 (median)	[A]Supervised [B]outpatient [C]Isokinetic [D]8-10 reps max flex % ext @ $60^{o}\cdot s^{-1}$ 4 x $180^{o}\cdot s^{-1}$ until exhaustion [E]20 min [F]3 x per week [G]1.75 months	**Body comp**: Thigh muscle cross sectional area **Strength**: Quadriceps peak torque	+ 7 % ‡ + 15 % ‡	0.30 S 0.49 M
Miller, 1987	1 group intervention	KTx (*n* = 10)	17	[A]Supervised & unsupervised [B]? & home based [C]Aerobic (walking & cycling) [D]40% - 60% max heart rate [E]25 – 40 min [F]3 x per week [G]25 - 26 months	**Kidney function**: Serum creatinine **Exercise capacity**: Multiples of resting metabolic rate **Blood Pressure:** Systolic blood pressure	+ 17 %[ns] + 114 % ‡ + 5 % [ns]	0.50 M 3.05 L 0.33 S

Horber, 1985	1 group intervention	KTx (n = 12) Control leg (n = 12)	6 (minimum)	[A]Supervised [B]Outpatient [C]Isokinetic [D]8-10 reps max flex % ext @ $60^{o} \cdot s^{-1}$ 4 x $180^{o} \cdot s^{-1}$ until exhaustion [E]20 min [F]3 x per week [G]1.8 months	**Body comp**: Thigh muscle cross sectional area: exercised vs. non-exercised leg **Strength**: Quadriceps strength (peak torque, 60 deg/s)	+ 8 % ‡ + 22 % ‡	0.31 S 0.50 M

When possible only data for the exercising kidney transplant patients are presented. ‡, significant vs. baseline value ($p < 0.05$); [ns], non significant; ?, insufficient information provided by author; KTx, kidney transplant patient; A, supervision; B, setting; C, mode; D, intensity; E, duration; F, frequency; G, length; vS, very small effect; S, small effect; M, medium effect; L, large effect. See Methods for further explanation of statistics.

Table 2.4. Effect of exercise interventions on outcomes in kidney transplant patients (with a comparable control group)

Author	Design	Groups	Transplant vintage (months)	Prescription	Outcome	% change in exercise vs. control[significance of within group main effect/interaction]	Interaction effect size
You, (2008)	Controlled trial	Exercise (*n* = 15) Control (*n* = 14)	?	**Exercise:** [A]Supervised & unsupervised [B]Outpatient & home based [C]Breathing, strength & flexibility [D]60 min [E]? [F]4-6 x per week [G]2.25 months **Control:** Normal routine care	**Lipids**: Serum cholesterol **Kidney function**: Serum creatinine **Strength**: Grip **Flexibility**: Sit and reach **Quality of Life**: ?	- ? [?/*] - ? [?/*] + ? [?/*] + ? [?/*] + ? [?/*]	? ? ? ? ?
Korabiewska, (2007)	Controlled trial	Exercise (*n* = 35) Control (*n* = 32)	1	**Exercise**: First six months: [A]Supervised & unsupervised [B]Inpatient & home based [C]Muscle strengthening, breathing, coordination, isometric & relaxation. [D]? [E]20-30min [F]2-3 x per week [G]12 months After 6 months: [C] Walking	**Strength**: Hand grip strength **Flexibility**: Right radiocarpal joint extension **Lung function**: Peak expiratory flow **Kidney function**: Serum creatinine	+ 16 vs. + 6 % [?/?] + 23 vs. + 10 % [?/?] + 23 vs. + 10 % [?/?] - 27 vs. - 41 % [?/?]	0.15 S 0.26 M 0.30 M 0.17 S

				[D]Submaximal intensity [E]10-20 min [F]1-3 weeks [G]6 months **Control**: Normal routine care			
Juskowa, (2006)	Randomised controlled trial	Exercise (n = 32) Control (n = 37)	2 days	**Exercise**: [A]Supervised & unsupervised [B]Inpatient [C]Muscle strengthening, breathing, coordination, isometric & relaxation [D]? [E]30 min [F]7 x week [G]1-1.25 months **Control**: Normal routine care	**Atherosclerosis markers**: Total homocysteine **Immune function**: Interleukin 18 **Lipids**: Total cholesterol High density lipoprotein cholesterol **Diabetes**: Fasting glucose	- 15 vs. + 23 % ‡/? + 8 vs. - 12% ns/? + 25 vs. + 27% % ‡/? + 29 vs. + 6 % ‡/? - 19 vs. - 23 % ‡/?	0.15 S 0.18 S 0.03 vS 0.31 M 0.10 S
Painter, (2003)	Randomised controlled trial	Exercise (n = 51) Control (n = 45)	1	**Exercise:** [A]Unsupervised [B]Home based [C]Aerobic (walking & cycling) [D]60-80% max heart rate [E]< 30 min [F]< 4 x per week [G]11 months **Control**: Normal routine care	**Blood pressure**: Systolic Diastolic **Lipids**: Total cholesterol High density lipoprotein cholesterol **Exercise capacity**: Multiples of resting metabolic rate **Body composition**: Body mass index	- 1 vs. - 4 % ns/ns + 3 vs. + 3 % ‡/ns + 14 vs. + 14 %‡/ns + 19 vs. 8 %‡/ns (p=0.07) + 19 vs. 4 %‡/* + 12 vs. 8 % ‡/ns	0.10 S 0.02 vS 0.00 vS 0.16 S 0.25 M 0.10 S

Author	Design	Groups	Transplant vintage (months)	Prescription	Outcome	% change in exercise vs. control[significance of within group main effect/interaction]	Interaction effect size
Painter, (2002)	Randomised controlled trial	Exercise (*n* = 54) Control (*n* = 43)	"Within 2"	**Exercise:** [A]Unsupervised [B]Home based [C]Aerobic (walking & cycling) [D]60-80% max heart rate [E]< 30 min [F]< 4 x per week [G]11 months **Control**: Normal routine care	**Exercise capacity:** VO^2 peak Physical activity on VO^2 peak by correlation (*r*) **Strength:** Quadriceps: peak torque **Body composition**: Fat mass Lean body mass **Quality of Life**: Short Form-36: physical functioning Role physical Physical component scale **Kidney function:** Serum creatinine **Blood pressure:** Number of medications	+ 25 vs. + 7 % ‡/* 0.24 ‡ + 32 vs. + 19 % ‡/* + 24 vs. + 30 % ‡/ns + 1 vs. + 3 % ‡/ns + 25 vs. + 14 % ?/ns (p=0.06) + 52 vs. + 12 % ‡/ns + 17 vs. + 10 % ‡/ns - 12 vs. + 13 % ns/ns + 15 vs. + 20 % ns/ns	0.30 M 0.24 S 0.20 S 0.08 vS 0.05 vS 0.20 S 0.19 S 0.17 S 0.16 S 0.08 S
Gonzalez-Molina, (1993)	3 month dietary intervention then randomised controlled trial	Exercise (*n* = 20) Lovastatin (*n* = 20)	?	**Exercise:** [A]? [B]? [C]Aerobic (walking) [D]? [E]? [F]? [G]3 months **Lovastatin**: 20mg/day	**Lipids:** Total cholesterol High density lipoprotein cholesterol	+ 5 vs. - 21 % ns/? + 4 vs. + 22 % ns/?	0.94 L 0.29 M

‡, main effect of time or significant correlation ($p < 0.05$); *, significant interaction ($p < 0.05$); ns, non significant main effect of time or interaction; ?, insufficient information provided by author; KTx, kidney transplant patient; A, supervision; B, setting; C, mode; D, intensity; E, duration; F, frequency; G, length; vS, very small effect; S, small effect; M, medium effect; L, large effect. See Methods for further explanation of statistic.

CHAPTER 3

Progressive Resistance Forearm Exercise for Arteriovenous Fistula Maturation in Chronic Kidney Disease Patients: A Feasibility Study.

Source of funding: This study was supported by unrestricted grants from the North West Wales National Health Service Trust Endowment Fund and by North Wales National Health Service Trust Research and Development-Central Area.

Abstract

Background. Approximately half of arteriovenous fistuale fail to mature for haemodialysis use accentuating the need for interventions to enhance fistula success and maturation. This study aimed to investigate the feasibility and effect of a post operative forearm exercise protocol on fistula vessel diameters and blood flows, success and maturation.

Methods. In this controlled feasibility trial, 31 participants were randomly allocated to either an EXERCISE (Mean (SD): 52 (14) years) or a CONTROL (60 (11) years) group following fistula surgery. EXERCISE involved a home based progressive resistance forearm exercise programme over 8 weeks. Exercise was prescribed four days /week for 30 minutes at an intensity perceived as 'somewhat hard' to 'hard'. CONTROL received routine care. Primary outcomes included fistula artery and vein diameters and blood flows by duplex ultrasound, fistula success and maturation. Secondary outcomes were maximal isometric handgrip strength and forearm muscle circumference. Outcomes were measured one day, four and eight weeks post surgery. Feasibility was determined based on outcomes relating to the methodological process, resources, management and treatment effects.

Results. EXERCISE had no effect on arterial diameter (95% CI, -0.24 [-1.12; 0.51] mm; small effect size) or venous diameter (95% CI, 0.16 [-1.84; 1.24] mm; trivial effect size) with small and trivial effect sizes reported respectively. Due to difficulties obtaining reliable readings, changes in blood flow were not analysed. Nineteen percent and 33% of fistulae failed in EXERCISE and CONTROL respectively. EXERCISE did not affect maturation time (95% CI, 1 [-16; 28] days). EXERCISE increased handgrip

strength (95% CI, 4.5 [0.5; 8.0] kg) but not forearm muscle circumference (95 % CI, 0.8 [-1.9; 3.4] cm). The study was deemed feasible with modifications.

***Conclusions*.** This feasibility study infers post operative forearm exercise to have no effect on fistulae vasculature parameters, success or maturation. A similar protocol implemented *before* arteriovenous fistula creation, however, is hypothesized to enhance surgery success and maturation. Registered as a clinical trial *NCT01061008*.

Introduction

The provision of good quality access remains a fundamental component of haemodialysis treatment. Current guidelines recommend an arteriovenous fistula (AVF) as the first choice of access (National Kidney Foundation,1997) with British Renal Association standards advocating for 65 - 85% of haemodialysis patients dialysing via this form of access (Fluck & Kumwenda, 2011). Arteriovenous fistulae are recognized as a superior form of access as they allow higher blood flows during dialysis, thus enhancing haemodialysis adequacy (Allon & Robbin, 2002). They also present with a lower risk of thromboses and lower intervention rates (Perera *et al.*, 2004), lower infection rates (Nassar & Ayus, 2001) and lower hospitalisation, morbidity and mortality rates (Dhingra *et al.*, 2001) in comparison to other forms of access such as arteriovenous grafts and permanent cuffed central venous catheters. Yet, despite these guidelines, in the United Kingdom only 40% of patients commence haemodialysis via an AVF (Fluck, 2011). This is in part due to high failure rates with up to 53% of AV fistulae failing to mature for the use of haemodialysis (Robbin *et al.*, 2002; Wong *et al.*, 2011). Interventions to enhance the chances of AVF maturity are therefore sought after.

Post operative forearm exercise could be such an intervention. Previous observations have verified that successful AVF maturation is more likely in fistulae with greater postoperative vascular diameters and blood flows (Robbin *et al.*, 2002, Kim *et al.*, 2001). These vasculature parameters could be increased through post operative forearm exercise with the rationale that firstly, the hyperaemic response to exercise elevates shear stress on the endothelial wall thus initiating vessel remodeling and arteriogenesis (Prior, Yang & Terjung, 2004). Secondly, if vessel diameter is enlarged then blood flow should also increase as the resistance to flow through a vessel is

inversely proportional to the fourth power of the radius (McDonald, 1974). Current guidelines recommend post operative forearm exercise for AVF maturation.However, this guideline is of opinion and there little evidence in its support (National Kidney Foundation, 1997). Previous research investigating hand grip exercise on forearm vasculature parameters in chronic kidney disease patients has shown disparate findings (Kumar *et al.*, 2010; Leaf *et al.*, 2003; Oder, Teodorescu & Uribarri, 2003; Rus *et al.*, 2005; Rodriguez Moran *et al.*, 1984). Furthermore, these studies have implemented exercise interventions prior to AVF creation (Kumar *et al.*, 2010; Leaf *et al.*, 2003) or on fistulae that have already matured (Oder, Teodorescu & Uribarri, 2003; Rodriguez Moran *et al.*, 1984). There are no known studies that have investigated the effect of postoperative forearm exercise on AVF vasculature parameters during the maturation phase.

This feasibility study aimed to implement an eight week progressive resistance hand grip exercise programme immediately following AVF creation in CKD patients. As this type of study has not previously been carried out, the objective of this randomised controlled investigation was firstly, to assess the feasibility of the methodological processes and procedures for later use on a large scale multicentre trial. Secondly, to determine the effect sizes of the eight week exercise intervention on AVF vessel diameters and blood flows, success and maturation.

Methods

Study Design. This feasibility study was a two-centre, single blind, pre test post test, randomised controlled trial registered on clinicaltrials.gov as NCT01061008. Participants were randomly allocated to a progressive resistance handgrip exercise group or a control group using opaque envelopes in a 1:1 manner, stratified by gender, centre, AVF type (radial or brachio – cephalic) and surgeon.

Participants. Stage four and five CKD patients were recruited from two renal units in North Wales, United Kingdom. Recruitment was co-ordinated through the vascular nurse at each centre. Eligible patients presented with Stage 4 of 5 CKD scheduled to have a native AVF fashioned in the arm. Patients were excluded if they were below 18 years of age; their clinician deemed them unable to withstand transiently raised systolic blood pressure by 35 mmHg, and diastolic by 25 mmHg; presented with contraindications to take part in forearm handgrip exercise or were unable to provide informed consent. Ethical approval was provided by Betsi Cadwaladr University Health Board Ethics Committee. All participants provided written informed consent.

Interventions. Patients allocated to the exercise group carried out progressive handgrip exercises post operatively over an eight week period. On the same day immediately post operation patients were asked to flex and extend their fingers and start squeezing a rubber ball with the fistula arm as tolerated due to pain from the surgery. As soon as the patient was comfortable squeezing the rubber ball they commenced training utilizing a handgrip trainer (Ironman Pro, www.ironmanfitness.com, **Figure 3.1.**) with six intensity settings which allowed for progression in exercise intensity with gains in strength. The intensity quantification of each setting was determined using a tension load cell (Model 615 S, Tedea Huntleigh, Vishay, Basingstoke, UK) connected to the

spring loaded piston of the hand grip device (**Figure 3.2**). Participants were asked to exercise at least four days per week for 30 minutes, contracting the handgrip device at a rate of 30 repetitions per minute at an intensity relating to a rating of perceived exertion (RPE) of 14 on the 6-20 Borg scale (Borg 1982). When 30 minutes of exercise could be completed at an RPE below 14, exercise intensity was increased to the next setting of the hand grip device. Exercise was supervised by an exercise physiologist during the first week and was then carried out unsupervised at home, with patients completing daily exercise diaries over the eight week period. Weekly phone calls were made to monitor compliance and address any problems or queries.

Patients allocated to the control group received routine care. However, they were restricted from using rubber squeeze balls for forearm exercise.

Outcomes. Outcome measures were assessed one day, four weeks and eight weeks post operatively. To avoid harms, secondary outcome measures of handgrip strength and forearm circumference were assessed pre surgery rather than one day following surgery.

Vascular Diameter and Volume Blood Flow. The primary outcome measure was AVF feeding artery and draining vein diameters. Volume flow through these vessels was also recorded as a secondary outcome measure. These measurements were taken by either a recently trained member in the research team (DK) or an experienced vascular sonographer (GR). Measurements were made using duplex ultrasonagraphy (iU22 xMatrix Diagnostic Ultrasound System, Phillips, WA,USA) with a linear array transducer (L17-5) at a frequency of 7 MHz. Ultrasound examination was performed in a warm environment with the patient seated in an upright position, the arm comfortably supported at 45˚ from the body. Measurements were made at predetermined distances 5 – 10 cm from the anastomosis (dependent on wound dressings and turbulent flow

around the anatomosis). The scanning position for each patient was traced using transparent sheets which allowed analogous measurement positions for all scans.

Cross sectional vascular diameter measurements were made using conventional grey scale B Mode imaging. Diameters were measured from the inner edges of the vascular wall (Wiese & Nonnast-Daniel, 2004). An adequate test re – test reliability was reported for this measure with an ICC of 98% and a coefficient of variation (CV) of 4% determined from six different measurements from three individuals made on two separate occasions on the same day. The inter-rater reliability between the recently trained member of the research team and an experienced sonographer for this measurement was 90%, with a CV of 17%.

Volume flow in the longitudinal plane was acquired using pulse wave Doppler ensuring that sample volume covered the entire width of the vasculature and a complete angle of isonation ≤ 60° in order to detect a substantial Doppler shift frequency (Thrush, Hartshorne 2010). The inter-rater reliability between the recently trained member of the research team (DK) and an experienced sonographer (BHJ) for this measurement was only moderate (75%) with a high CV (20%). Due to the high variability of one off flow measurements (CV= 26%) measurements were carried out 3 times and averaged. Examples of vasculature images obtained by DK are displayed in **Figure 3.3.**.

Maturation. A fistula was deemed mature according to either the KDOQI 'rule of 6' when the diameter of the draining vein was > 6 mm and presented with flows > 600 ml/min (National Kidney Foundation, 1997) or when an experienced vascular nurse, who was blinded to group allocation, deemed maturation had occurred. Experienced vascular nurses have shown to have an 80% success rate in determining fistula maturation (Robbin *et al.*, 2002). Arteriovenous fistula failure was declared if the patient was relisted for another surgery within the eight week study period.

Handgrip Strength. Maximal hand grip strength was determined using a handgrip dynamometer (5001A, Takei Co., Tokyo, Japan). Following a warm up at 50% and 75% of the estimated maximal voluntary contraction, three maximal contractions of 2-3 seconds were performed and the peak value recorded.

Forearm Circumference. Assuming a circular limb and muscle compartment, a symmetrically distributed fat rim and including bone correction, forearm circumference was determined by anthropometry (Heymsfield *et al.*, 1982).

Harms. Information on harms including joint, muscle or wound pain was recorded by the patient in their training diaries and also collected actively by the researcher during each weekly phone call to the patient. Other unexpected and serious (fatal, life threatening, or resulted in hospitalization) harms were collected passively as they occurred and during the trial period only.

Feasibility. The main feasibility outcome was as either i) Stop – main study not feasible; ii) Continue but modify protocol – feasible with modifications; iii) Continue without modifications but monitor closely – feasible with close monitoring and iv) Continue without modifications – feasible as is (Thabane *et al.*, 2010). This outcome was assessed at the end of the study and was based on the following:

Process. Feasibility of processes that are key to the success of the main study included assessments on willingness of consultants to recruit patients, recruitment rates, consent rates, acceptability of group allocation and compliance with the specified interventions.

Resources. Assessments on time and resource problems were based on the time to collect the data, the average time that patients were on surgical waiting lists before AVF surgery and the availability of ultrasound facilities at each centre.

Management. Assessment of human and data optimization problems included the ability of members of the research team to collect ultrasound data as compared to trained vascular sonographers and the amount of associated missing data.

Scientific. The feasibility of treatment effects were based on the estimated effects of forearm exercise on the predefined outcome measures and the variance of such effects. Safety was based on the number of harms reported as a direct result of implemented interventions.

Statistical Analyses. Data analyses were carried out separately for type of AVF (radiocephalic or brachiocephalic) due to a possible difference in effect sizes based on the differing vessel sizes of these two types of AVF. Outcome measures of maturation and success as well as harms were analysed on an *intention to treat* basis. All other outcomes were analysed on a *per protocol* basis.

Data on feasibility and harms were presented descriptively only. As the purpose of this study was to observe possible estimated effects and the variance of the outcome measures, data was analysed for effect sizes and 95% confidence intervals rather than statistical significance. As recommended for feasibility studies of this size, median estimates and 95% confidence intervals representing upper and lower bound limits of the difference between the medians of change scores across groups were calculated using the Hodges and Lehman method. Effect sizes (r) were also calculated based on the assumption of non parametric data (Field, 2009), and were interpreted as trivial < 0.3; small ≥ 0.3, medium ≥ 0.5 or large ≥ 0.8 (Cohen, 1988). Weekly training load data were analysed using a 2 x 8 (group x time) repeated measures ANOVA with $p \leq 0.05$ denoting statistical significance. Confidence interval data are presented as median values. All other data are presented as mean (standard deviation). A formal sample size estimation was not completed for this feasibility study.

Results

Participants. Patients were recruited between May 2008 - October 2008 and September 2010 – January 2012. Participant flow throughout the study is shown in **Figure 3.4.** During this period a total of 75 surgeries for creation of a primary AVF occurred between both centres, with 63 of these patients assessed for eligibility.

Of patients allocated to the exercise group 13 received radiocephalic fistulae and 3 received brachiocephalic fistulae. Of the patients allocated to the control group, thirteen patients received radiocephalic fistulae and 2 received brachiocephalic fistulae.

Of the 13 patients who received radiocephalic fistulae allocated to the control group, four patients were lost to follow up due to medical complications (n=1) and loss of interest (n=3). Of the 13 patients who received radiocephalic fistulae allocated to exercise group, two patients were lost to follow up due to death (n=1) and loss of interest (n=1). Of the 5 patients who received brachicephalic fistulae, both patients allocated to the control group failed. Therefore, brachiocephalic fistulae were omitted from the analyses due to an unviable sample size. Thus, analyses of outcome measures were carried out in nine and 10 patients allocated to the control and exercise groups respectively. Participant characteristics are displayed in **Table 3.1.**

Consultants at both centres were willing to recruit patients. With 9/9 (100%) eligible patients approached by consultants and 16/35 (46%) approached by a member of the research team consenting to participate in the study, recruitment was more successful when patients were informed about the study by their consultant rather than a member of the research team.

Training Load and Compliance. Training load, displayed in **Figure 3.5.**, increased over the eight week training period as evidenced by a significant main effect over time ($p = 0.004$).

Only one patient allocated to the exercise group did not accurately complete an exercise diary. Patients completed 94 (10) % of the required exercise sessions. The only reason for missing sessions was illness (9 sessions).

Vascular Diameters

Arterial Diameter. As depicted in **Table 3.2**. and **Figure 3.6**., the increase in arterial diameter from Week 0 to Week 8 was the same in both the exercise and control groups. The median difference and 95% confidence interval of absolute change values between the exercise and the control group was -0.24 [-1.12; 0.51] mm.

In Week 0 to Week 4 increases in arterial diameter were the same in both the exercise and the control group with a small effect size observed ($r = 0.3$). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was 0.30 [-0.30; 1.25] mm.

In Week 4 to Week 8 the increase in arterial diameter was larger in the control group compared to the exercise group with a large effect size observed ($r = -0.80$). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was -0.63 [-1.09; -0.13] mm.

Venous Diameter. As depicted in **Table 3.2.** and **Figure 3.7.**, the increase in venous diameter from Week 0 to Week 8 was the same in the exercise group compared to the control group with trivial effect sizes observed. The median difference and 95% confidence interval of absolute change values between the exercise and the control group was 0.16 [-1.84; 1.24] mm.

In Week 0 to Week 4 increases in venous diameter were the same in both the exercise group and the control group with a small effect size observed ($r = 0.3$). The

median difference and 95% confidence interval of absolute change values between the exercise and the control group was -0.04 [-1.14; 0.77] mm.

In Week 4 to Week 8 the increase in venous diameter was the same across both the exercise and groups with trivial effect size observed (r = -0.09). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was -0.34 [-1.90; 0.86] mm.

Feeding Artery and Draining Vein Blood Flows. Members of the research team sought difficulty in obtaining volume flow measurements. A total of 60 scans were completed throughout the trial, 46 of these by members of the research team and 14 of these by a trained sonographer. Adequate flow measurements were obtained in 14/14 (100%) of scans carried out by the sonographer and only 28/46 (60%) scans carried out by members of the research team. This resulted in missing blood flow data in 7/11 (64%) participants who were included in the per protocol analysis. Due to this high proportion of missing data it was not possible to analyse the outcome measure of blood flow.

Arteriovenous Fistula Success and Time to Maturation. Three of 16 (19%) and 5/15 (33%) of fistulae failed in exercise and control groups, respectively. Reasons for failing fistulae are described in **Table 3.3.**. Time to maturation was 41 (13) days in the exercise group and 38 (14) days in the control group with a trivial effect size observed (r = 0.2). The median difference and 95% confidence interval of maturation days between the exercise and the control group was 1 [-16; 28] days.

Hand Grip Strength. From Week 0 to Week 8 hand grip strength increased in the exercise group and decreased in the control group with medium effect sizes observed (**Table 3.2.**). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was 4.5 [0.5; 8.0] kg.

In Week 0 to Week 4 hand grip strength increased in the exercise group and decreased in the control group with medium effect sizes observed (r = 0.55). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was 6.0 [-0.5; 11.0] kg.

In Week 4 to Week 8 handgrip strength increased in a similar manner across both groups with trivial effect sizes observed (r = -0.11). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was -1.0 [-6.0; 4.0] kg.

Forearm Muscle Circumference. From Week 0 to Week 8 forearm muscle circumference remained the same across both groups with trivial effect sizes observed (**Table 3.2**). The median difference and 95% confidence interval of absolute change values between the exercise and the control group 0.8 [of -1.9; 3.4] cm.

In Week 0 to Week 4 forearm muscle circumference was the same across both groups with trivial effect sizes observed (r = -0.27). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was 0.5 [-2.2; 4.9] cm.

In Week 4 to Week 8 forearm circumference was the same across both groups with trivial effect sizes observed (r = 0.13). The median difference and 95% confidence interval of absolute change values between the exercise and the control group was -0.7 [-2.6; 2.2] cm.

Harms. Harms reported during exercise sessions were tender thumb and fingers (3 sessions) and a sharp pain in the AVF area (1 session). These harms were resolved without late effects or sequalae and did not prevent patients from continuing their allocated intervention. One patient in the exercise group was advised against starting the exercise intervention due to a complicated wound following surgery. Two patients from the exercise group were hospitalised during the eight week period following surgery due

to reasons unrelated to the exercise interventions. One of these patients died during the hospitalisation period. One patient from the control group dropped out five weeks following AVF surgery due to medical complications unrelated to the their allocated intervention.

Feasibility. This study was deemed as feasible with modifications. Modifications and considerations that should be taken into account to run a large scale multicentre trial are discussed herein.

Discussion

This study aimed to assess the feasibility of running a large scale multicentre trial on the effects of hand grip exercise on AVF vasculature parameters and maturation. The study was deemed feasible provided the following modifications and considerations are taken into account.

1) Process

1.1) In order to enhance recruitment and consent rates consultants should approach patients to inform them about the study rather than a member of the research team. One hundred percent of patients who were approached by their consultant consented to take part in this trial compared to 46% approached by a member of the research team. This supports previous findings that have shown that patients are more likely to take part in a trial if their regular clinician discusses research options with them (Harris Interactive, 2005).

1.2) In this study 15% of patients who received an AVF were not assessed for eligibility. In order to prevent this loss of potential recruitment opportunities, correspondence regarding surgery dates and times should be carried out through the administrative staff of the surgeon as well as the vascular nurse.

1.3) As current guidelines suggest distal placement of fistulae to preserve vasculature (National Kidney Foundation, 2006) the trial should focus on radiocephalic over brachiocephalic fistulae as higher numbers of these procedures would be expected. This is reflected in this study whereby 84% of consenting patients were scheduled to receive a radiocephalic fistula.

1.4) Failure rates (26% of consenting patients) and hospitalisation incidents (10% of consenting patients) across both groups should be considered when planning a sample size.

1.5) Compliance to the exercise intervention was shown through objective significant increases in weekly training load as well as the medium effect sizes observed for increases in handgrip strength in the exercise group over the eight week intervention period. Furthermore, patients allocated to the exercise group completed 94% of scheduled sessions. This high compliance is possibly a result of the home based nature of the exercise programme with patients being able to exercise at personally convenient times at home or during dialysis sessions. Home based and intradialytic exercise programmes have previously reported higher compliance rates in comparison to supervised outpatient programmes (Konstantinidou *et al.*, 2002).

2) Resources

2.1) Over a time period of 20 months, 11 complete data sets were available for per protocol analysis. However, 87 surgeries were scheduled during the period of this trial; therefore, if recruitment success is enhanced by taking on abovementioned recommendations (1.1 and 1.2) then it is possible that a larger sample could be collected in this time frame.

2.2) Over the duration of this study the average time that patients were on the surgical waiting list for AVF creation was 82 ± 60 days. Due to high hospitalisation rates in CKD stages four and five with 45% - 69% of patients being hospitalised annually (USRDS, 2011; USRDS, 2012), it is possible that patients may be hospitalised whilst on the waiting list for AVF surgery. If patients are recruited onto the study as soon as they are listed for surgery their eligibility criteria should be reassessed prior to surgery in the event of a hospitalisation whilst on the waiting list.

2.3) Ultrasound resources were readily available at all centres with the same ultrasound equipment utilised by both centres. If a multicentre trial were to be implemented the compatibility of different scanning equipment between centres should be assessed.

3) Management

3.1) A large amount of missing data relating to arterial and venous blood flows resulted from the inability of members of the research team to collect this measure reliably. As experienced sonographers acquired this data accurately in 100% of their scans it is recommended that ultrasound measurements are carried out by an experienced vascular sonographer rather than a newly- trained research assistant. The Society of Vascular Technology in Britain and Ireland (http://www.svtgbi.org.uk) recommend at least one of the following qualifications to become fully competent in AVF surveillance: i) Full Society for Vascular Technology of Great Britain and Ireland accreditation; ii) Post graduate qualification in ultrasound imaging from a Consortium for Accreditation of Sonographic Education accredited course including arterial and venous module; iii) Level 3 radiologists with core training in vascular imaging; iv) Medical or surgical staff that have followed the Royal College of Radiologists recommendations for training in vascular scanning.

4) ***Scientific***

In general, the effects of exercise on AVF arterial and venous diameter were trivial to small. Previous reports of the inhibition of metalloproteinases responsible for arteriogenesis and the reduced generation of nitrogen oxide in uremic conditions have initiated discussions concerning a blunted flow mediated arterial enlargement in this disease state (Dammers *et al.,* 2005a). However, despite a diminished endothelial dysfunction, previous findings have reported increases in radial artery and vein diameter following forearm exercise in chronic kidney disease patients (Kumar *et al.*, 2010; Leaf

et al., 2003; Oder, Teodorescu & Uribarri, 2003; Rus *et al.,* 2005; Rodriguez Moran *et al.,* 1984). An explanation for the contradictory observations may lie in the timing of the exercise implementation. Previous studies have investigated changes in vasculature parameters prior to AVF creation (Kumar *et al.*, 2010), in fistulae that have been mature for more than three years (Rodriguez Moran *et al.,* 1984) or in non fistula arms (Leaf *et al.,* 2003; Oder, Teodorescu & Uribarri, 2003; Rus *et al.,* 2005) whilst the current study implemented hand grip exercise of the fistula arm during the maturation phase.

Increases in shear stress on the endothelial wall leads to vascular remodeling and arteriogenesis (Prior, Yang & Terjung, 2004). Following AVF formation chronic increases in flow result in shear stress increases for at least one year (Dammers *et al.*, 2005a; Dammers *et al.,* 2002; Ene-Iordache *et al.*, 2003). However, over time shear stress is normalised, supposedly due to structural adaptations of the arterial wall in response to increased shear stress (Girerd *et al.,* 1996). Increases in shear stress initiated by exercise hyperaemia prior to AVF formation or when the fistula has been mature for several years (and shear stress has been normalized) may explain the increases in vasculature diameter previously reported. On the other hand, during the maturation stage it has been suggested that there is a continued increased shear stress despite corrective arterial remodeling, inferring that the challenge imposed by chronic increases in blood flow exceed the vascular adaptation capacity (Dammers *et al.*, 2005a). With this rationale, further increases in blood flow from exercise induced hyperaemia during this stage would be futile.

In addition, AVF failure was similar across both forearm and exercise groups. It should be taken into consideration that apart from vessel diameter and blood flow there are many other factors that have been shown to predict AVF failure. These include vascular disease, heart failure, untreated hypertension, stroke history, gender, age, late referral, interopertaive heparin dose and surgical technique (Feldman *et al.*, 2003;

Ravani *et al.,* 2005), some of which may play a larger role than post operative vasculature diameter and blood flow in AVF success. Using optimum surgical technique, for example, has a predictive probability for maturation success as high as 84% (Feldman *et al.,* 2003). The number of variables affecting maturation may explain the large variability observed in the outcome measures.

The observations of effects and confidence intervals on the main outcome measures of this study are not in favour of implementing postoperative forearm exercise for AVF maturation. However, more emphasis is being placed on preservation of sites for vascular access (Fluck & Kumwenda, 2011). Pre surgical diameter and blood flow have been shown to influence the success of AVF surgery (Wong *et al.,* 2011). One randomized control trial has investigated the effects of chronic exercise on resting blood flows and forearm vessel diameters in CKD patients prior to AVF creation (Kumar *et al.,* 2010). That study reported significant increases in resting arterial blood flow velocities as well as increases in artery and vein diameters of 0.2 [0.1;0.3] mm and 0.6 [0.4;1.2]mm respectively. The exercise intervention implemented in that study lacked physiologically effective prescription parameters and therefore these reported benefits of exercise may even be underestimated. Furthermore, it is unknown whether these increases translated to enhanced AVF success and maturation. Based on such evidence and in combination with the observations of the current study, it is suggested that the exercise protocol proposed in the current study may be more beneficial if implemented before AVF surgery. As the average surgery waiting list time observed in the current study was 10 weeks, this provides an opportunistic window for an 8 week exercise prescription between surgery referral and AVF creation. It therefore appears to be more feasible to implement the methodological protocol carried out in the current study *before* AVF creation, observing the impact of any potential benefits on surgery outcome.

In conclusion, the findings of the current suggested that hand grip exercise immediately following AVF creation to have no effect on AVF vasculature parameters, success or maturation. A similar protocol, taking into account the suggested protocol modifications and implemented before AVF creation, however, is hypothesised to enhance surgery success and maturation.

Figure 3.1. Ironman adjustable handgrip device.

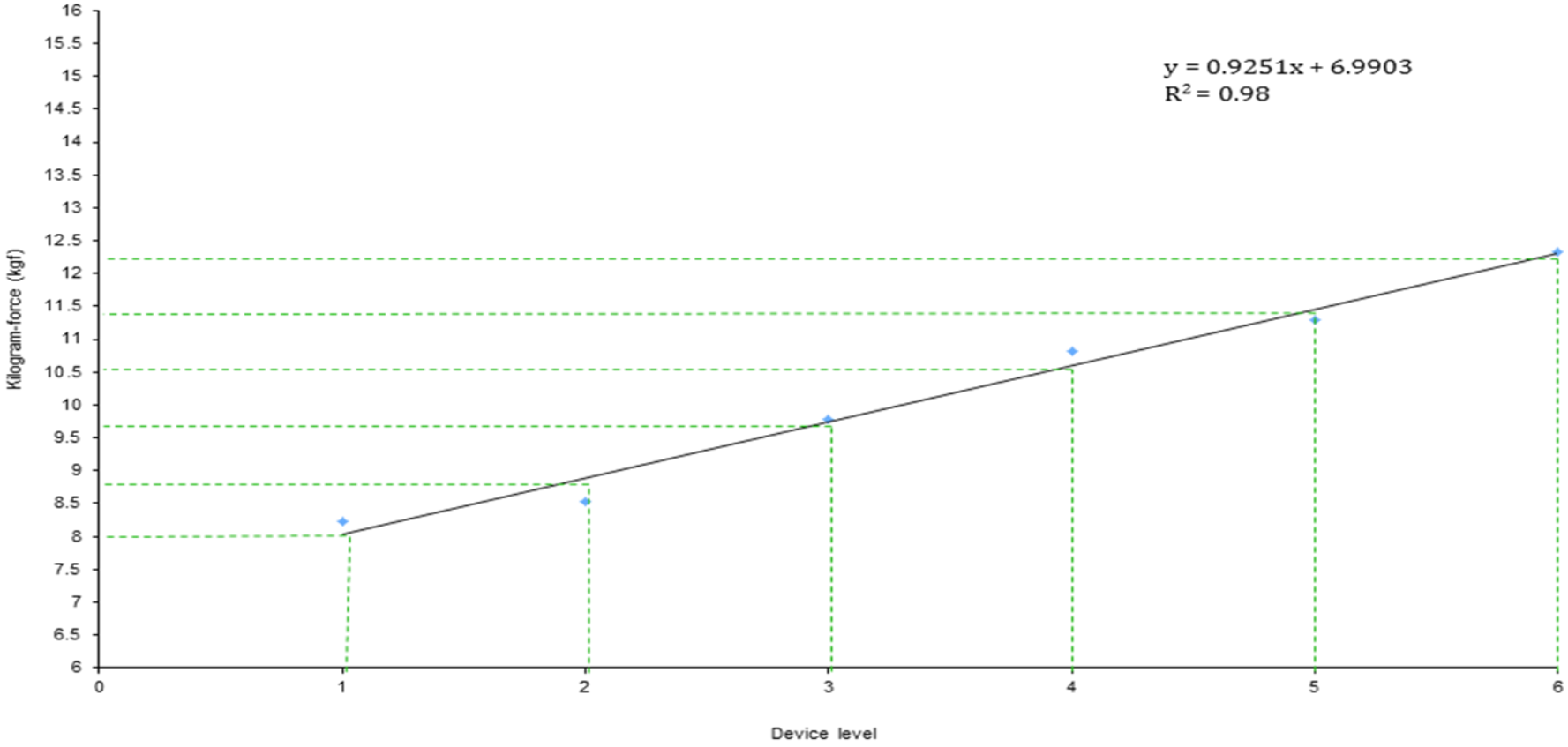

Figure 3.2. Quantification of setting intensity of the Ironman handgrip device. Adapted from Law (2008).

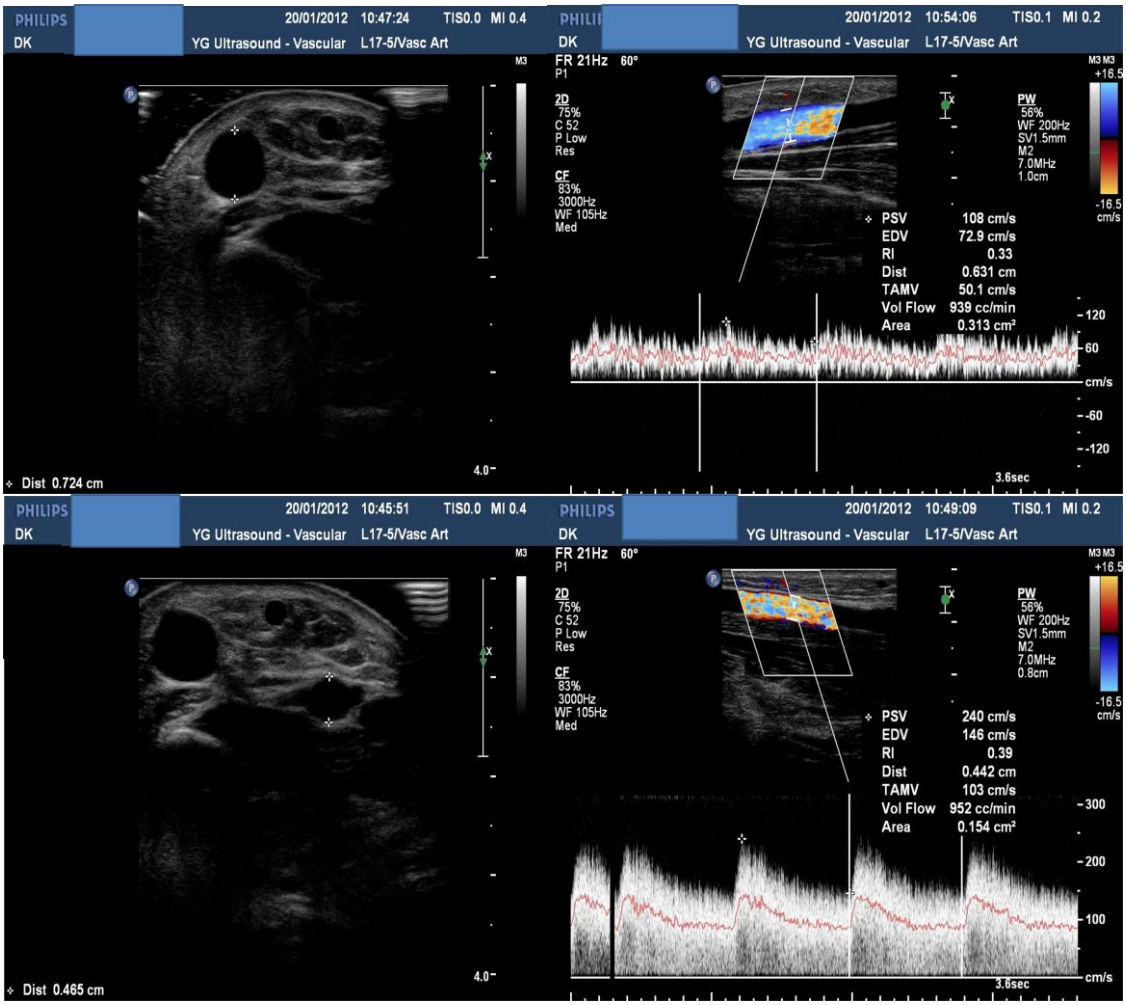

Figure 3.3. Vasculature of a mature AVF at 8 weeks post surgery. Images are taken 5 cm from the anastomosis. The cephalic vein diameter and flow are displayed in the top left and top right hand images, respectively. The radial artery and flow are displayed in the bottom left and right hand images ,respectively.

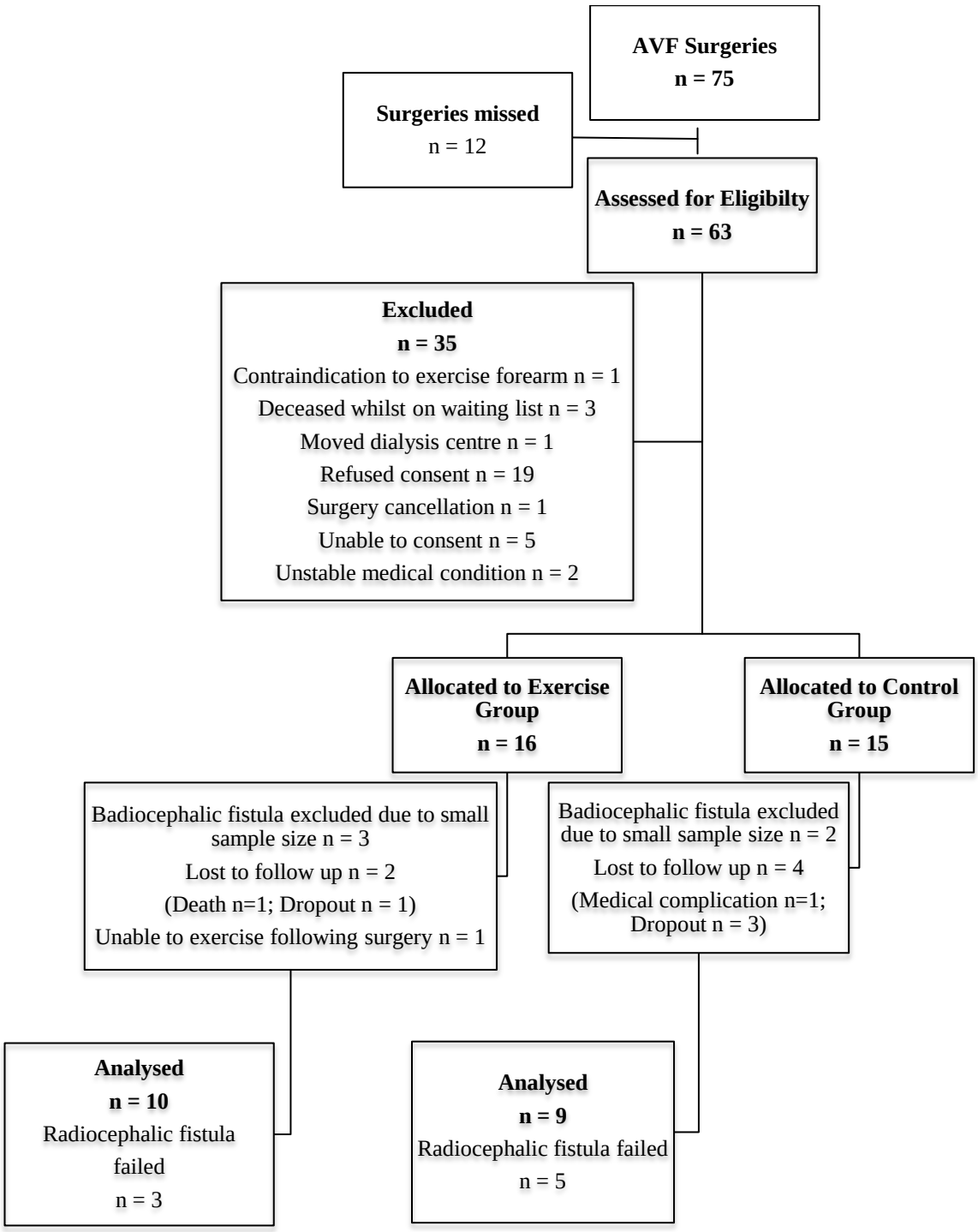

Figure 3.4. Participant flow throughout the study.

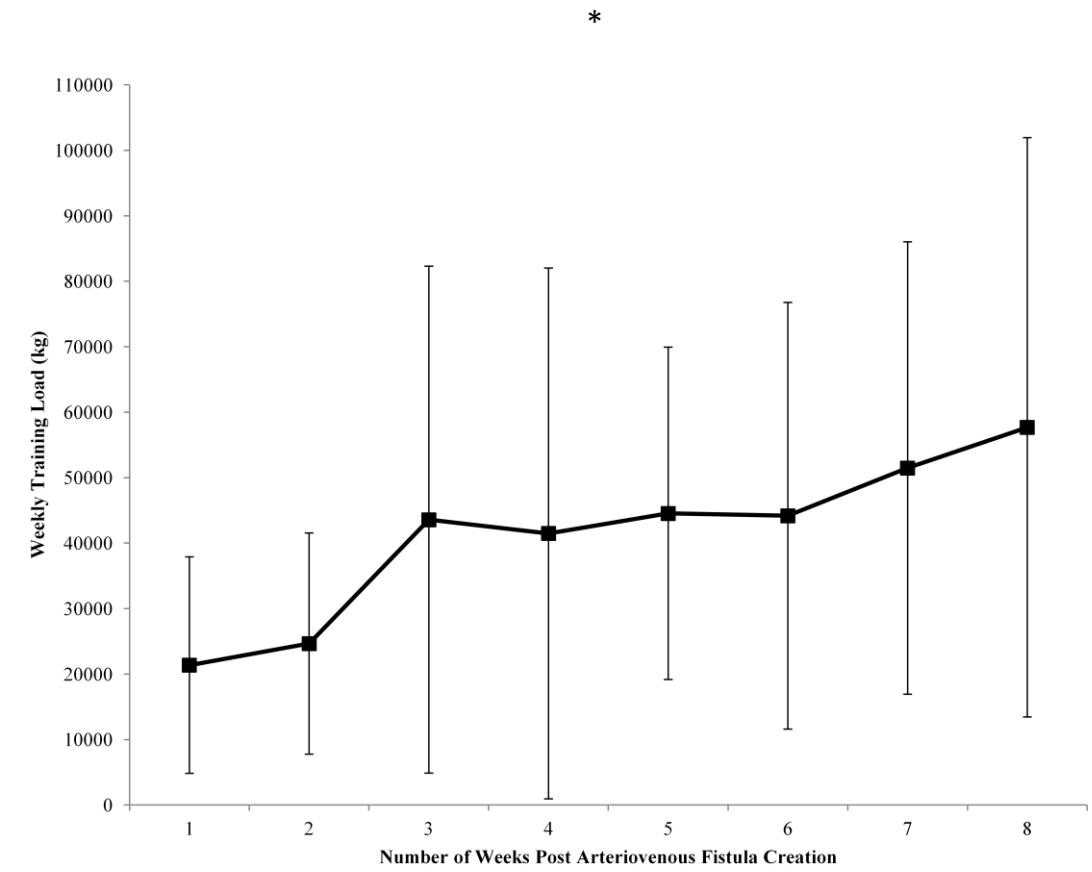

Figure 3.5. Weekly training load (repetitions x weight) of participants allocated to the forearm exercise group. *, significant main effect for time indicating an increase of training load over time (p = 0.004). Values are mean (SD).

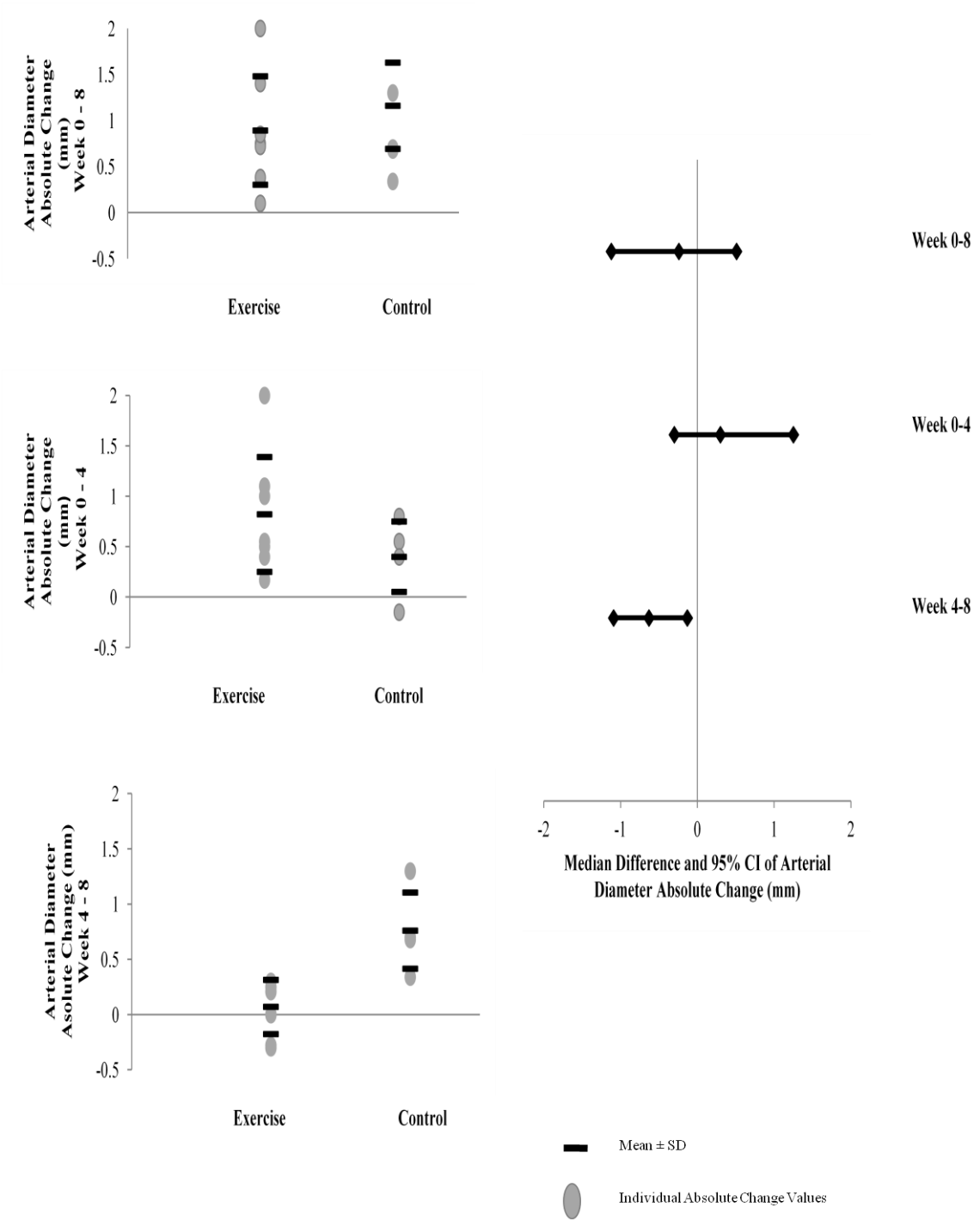

Figure 3.6. Absolute change in arterial diameter across forearm exercise and control groups at Weeks 0 – 4; 4 – 8 and 0 – 8 following arteriovenous fistula creation. Ninety-five percent confidence intervals represent lower and upper bound limits of the difference between the median of arterial diameter change scores across groups calculated using the Hodges and Lehman method (Kirkwood, Sterne & Kirkwood, 2003).

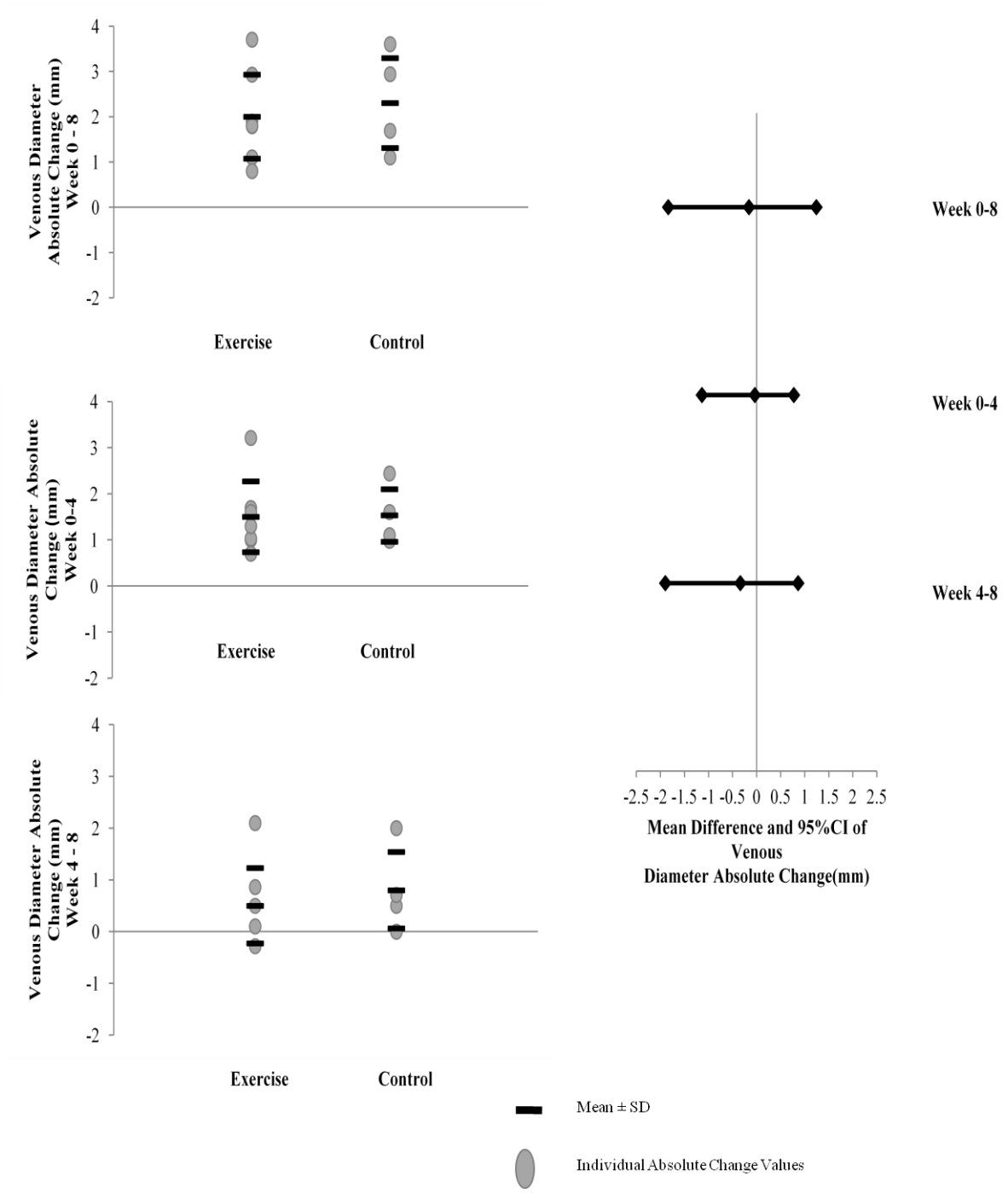

Figure 3.7. Absolute change in venous diameter across forearm exercise and control groups at Weeks 0 – 4; 4 – 8 and 0 – 8 following arteriovenous fistula creation. Ninety-five percent confidence intervals represent lower and upper bound limits of the difference between the median of arterial diameter change scores across groups calculated using the Hodges and Lehman method (Kirkwood, Sterne & Kirkwood, 2003).

Table 3.1. Participant characteristics across groups of *intention to treat* data.

	Exercise	Control
Demographics		
Age (years)	52 (14)	60 (11)
Gender (male/female)	11/5	11/4
BMI (kg/m^2)	27 (8)	26 (6)
CKD Stage:		
Four	7	7
Five	9	8
Aetiology of CKD:		
Arteriopathic	1	0
Congenital	2	1
Glomerulonephritis	5	9
Miscellaneous	8	5
Type of Renal Replacement Therapy:		
Haemodialysis	6	5
Peritoneal Dialysis	2	2
Transplant	1	1
Co-morbid Conditions:		
Diabetes	3	6
Ischemic Heart Disease	1	0
Hypertension	7	5
Smokers	4	3
Medication (tablets/day)		
Scheduled Arteriovenous Fistula Surgery Characteristics		
Arteriovenous Fistula Type:		
Brachiocephalic fistula	3	2
Radiocephailc fistula	13	13
Arteriovenous Fistula Attempt		
Haematology and Biochemistry		
Albumin (g/L)	41 (4)	37 (5)
Creatinine (umol/L)	268 (141)	367 (197)
Haemoglobin (g/dL)	10.7 (1.3)	11.4 (2.1)
Urea (mmol/L)	13.8 (7.7)	11.7 (6.5)

BMI, Body Mass Index; CKD, Chronic Kidney Disease.

Table 3.2. Data representing outcome measures collected for forearm exercise and control groups at 0, 4 and 8 weeks following arteriovenous fistula creation.

Outcome Measure	Exercise			Control			Effect Size (*r*)	Median [95% CI]
	Week 0	Week 4	Week 8	Week 0	Week 4	Week 8	Week 0-8	Week 0-8
Arterial Diameter (mm)	3.26 (0.68)	4.07(0.54)	4.14 (0.69)	3.17 (0.38)	3.57 (0.71)	4.32 (0.63)	Small	-0.24 [-1.12; 0.51]
Venous Diameter (mm)	3.77 (0.70)	5.28 (0.61)	5.78 (0.51)	4.09 (0.46)	5.62 (0.80)	6.42 (0.89)	Very Small	-0.16 [-1.84; 1.24]
Hand Grip Strength (kg)	32 (15)	34 (15)	35 (15)	37 (5)	34 (8)	35 (6)	Medium	4.5 [0.5; 8]
Forearm Muscle Circumference (cm)	11.05 (2.78)	11.27 (2.57)	11.28 (2.13)	9.48 (1.89)	8.7 (2.78)	8.88 (2.44)	Small	0.82 [-1.90; 3.40]

Values are Mean (SD). Effect Sizes were calculated and interpreted as Very Small < 0.3; Small > 0.3; Medium > 0.5 and Large > 0.8. Median estimates and 95% confidence intervals representing upper and lower bound limits of the difference between the medians of change scores across groups were calculated using the Hodges and Lehman method (Kirkwood, Sterne & Kirkwood, 2003). CI, confidence interval.

Table 3.3. Number of arteriovenous fistula failures, demographics of patients with failed fistulae and reasons for failure across both exercise and control groups.

	Exercise	**Control**
Number of Failed Arteriovenous fistulae	3	5
Age (years)	47 (9)	70 (10)
Gender (male/female)	2/1	2/3
Smokers (n)	0	1
Diabetics (n)	1	3
Reasons for Failure:		
Unsuccessful Surgery	0	3
Poor Vessel Development	3	2

Values are mean (SD).

CHAPTER 4

Dialysis Adequacy and Solute Removal: Effect of Intradialytic Exercise.

A Randomised Controlled Trial.

Source of Funding: This study was supported in part by an unrestricted grant from BBraun Avitum, Melsungen, Germany.

Abstract

Background. Dialysis adequacy is a significant predictor of hospitalisation and mortality in maintenance haemodialysis (HD) patients. Whether intradialytic exercise training can enhance dialysis adequacy is unclear.

Methods. In a single blind, controlled, randomised crossover study, 11 HD patients (mean (SD) age: 58 (13) years) completed three trial arms: normal routine care (CONT); increased HD time of 30 minutes (TIME); and intradialytic exercise (EXER), consisting of 60 minutes of cycling exercise at 95% of the lactate threshold in the last 90 minutes of HD. The primary outcome was equilibrated Kt/V_{urea}. Secondary outcomes included reduction and rebound ratios of urea, creatinine, phosphate and $beta_2$-microglobulin.

Results. Increased HD time, but not exercise, increased equilibrated Kt/V_{urea} compared to control trials (TIME vs. CONT: 95% CI, 0.15 [0.05; 0.26]; EXER vs. CONT: 95% CI, 0.03 [-0.05; 0.12]). Increased time also improved reduction ratios of urea and creatinine. In contrast, exercise, but not time, increased phosphate reduction ratio (EXER vs. CONT: 95% CI, 8.6 [0.5;16.7] %; TIME vs. CONT: 95% CI, 5.0 [-1.0; 11.1] %).

Conclusions. This is the first rigorously controlled study to compare intradialytic exercise and longer HD session time for dialysis adequacy. An extra 30 minutes of HD time significantly enhanced dialysis adequacy as determined by the primary outcome of equilibrated Kt/V_{urea}, but exercise only enhanced phosphate clearance. Thus intradialytic exercise cannot replace the traditional prescription of increased HD time, but may be a useful adjunctive therapy for serum phosphate control. Registered as a clinical trial *NCT01481688.*

Introduction

Haemodialysis remains the most popular form of renal replacement therapy with 65% of Stage 5 CKD patients receiving this treatment modality in the United States (USRDS, 2011). Haemodialysis adequacy as defined by urea clearance is a significant predictor of hospitalisation (Hakim *et al.*, 1994; Maiorca *et al.*, 1995) and mortality (Desai *et al.*, 2009). Previous methods of enhancing dialysis adequacy such as increasing the dose or frequency of dialysis sessions have been confronted with barriers of patient compliance and cost implications (Locatelli *et al.*, 2005). Improving dialysis adequacy remains a major challenge for nephrologists. Therapeutic strategies to enhance dialysis adequacy, including the removal of solutes other than urea are thus highly warranted (Vanholder & Glorieux, 2003; Dhondt *et al.*, 2000; Vanholder *et al.*, 2003).

One suggested strategy is to exercise during dialysis. Equation modelling to simulate intradialytic exercise predicts that the hyperaemia to low perfusion tissues such as muscle will increase urea clearance (Smye, Lindley & Will, 1998). Furthermore, it has been suggested that the increase in dialysis adequacy with 60 minutes of intradialytic exercise is equivalent to increasing dialysis time by 20 minutes (Kong *et al.*, 1999). However, previous studies investigating the effect of intradialytic exercise on solute removal have shown conflicting results (Kong *et al.*, 1999; Parsons, Toffelmire & King-VanVlack, 2004; Leung, 2004; Vaithilingam *et al.*, 2004; Parsons, Toffelmire & King-VanVlack, 2006) (**Table 4.1.**). The disparity in these findings may lie in differing exercise prescriptions with the timing, intensity and duration of exercise perhaps influencing solute clearance. For example, kinetic models imply that the majority of urea clearance occurs during the first half of dialysis (Leypoldt, 2005). If exercise were carried out during the second half of dialysis when lower plasma levels of urea are evident then a greater concentration gradient would be established between low

perfusion tissue and plasma, resulting in a greater diffusive flux in urea from the tissue to the plasma. In support of this speculation, it has been mathematically predicted that by sustaining high blood flow to low perfusion tissues in the latter part of dialysis, post dialysis urea rebound will almost be entirely eliminated (Smye, Lindley & Will 1998). Referring to exercise duration, previous observations (Kong *et al.*, 1999; Parsons, Toffelmire & King-VanVlack, 2004; Leung, 2004; Parsons, Toffelmire & King-VanVlack, 2006; Adorati, 2000) as well as simulative equations (Smye, Lindley & Will, 1998) imply that high blood flow to low perfusion tissues should be sustained for longer than 30 minutes to have any effect on solute clearance from the lean tissue. In summary, exercise should be carried out in the later part of dialysis at an intensity allowing the greatest amount of hyperaemia to be maintained over the longest possible duration. Exercise just below the anaerobic threshold, that carefully managed post exercise hypotension, would allow such an exercise prescription.

The purpose of this study was first, to implement an intradialytic exercise programme comprised of prescription parameters deemed most effective at enhancing dialysis adequacy, investigating its effects on small molecule, middle molecule and inorganic substance clearance. Second, to compare effects of intradialytic exercise to the traditional prescription of increasing dialysis time on solute removal. It was hypothesised that intradialytic exercise completed in the second half of dialysis would significantly increase solute clearance to the same extent as an extra 30 minutes of dialysis time.

Methods

Study Design. This controlled trial utilised a crossover design (clinicaltrials.gov: NCT01481688). Each participant carried out three trial arms: CONTROL, EXERCISE and TIME. Trial arm order was randomised (DK) using a computer-generated (www.randomizer.org) list of random numbers which were concealed in sealed opaque envelopes.

Participants. Patients were recruited between 01.07.2011 and 31.08.2011 from Gwynedd Hospital, UK. Eligible participants presented with Stage 5 CKD receiving haemodialysis three times per week. Participants were excluded if they presented with: age below 18 years; receiving routine haemodialysis for less than 3 months; contraindications to exercise; chronic access problems or recirculation; haemoglobin levels below 11 g/dL; persistent hypotension with pre-dialysis systolic blood pressures below 100 mmHg; episodic treatment induced hypotension with frequent drops in systolic blood pressure below 30 mmHg; unstable medical condition; or unable to provide informed consent. Ethical approval was obtained from Betsi Cadwaladr University Health Board Ethics Committee and the study adhered to the Declaration of Helsinki 2008. Participants provided written informed consent.

Interventions. Each patient participated in two haemodialysis sessions of each of the trial arms: CONTROL, EXERCISE and TIME.

CONTROL trials consisted of routine prescribed haemodialysis treatment.

EXERCISE trials involved cycling exercise using equipment (Rehab Trainer 881 E, Monark, Sweden) adapted (Living Life, UK) to fit the end of a dialysis chair (Stephen H Anatomical New, Garhen Bilance, Italy) (**Figure 4.1.**).

Before trials commenced, the lactate threshold was determined via the individualised anaerobic threshold technique (Stegmann, Kindermann & Schnabel, 1981). This involved a cycling submaximal exercise test consisting of 15 Watt

increments every 3 minutes (Koufaki, Naish & Mercer, 2001). Blood lactate sampling from the earlobe occurred at the end of each 3 minute stage until values around 6 mmol/L (Urhausen *et al.,* 1993) were reached. Lactate sampling continued every three minutes during the recovery until lactate levels dropped to peak levels during exercise. The point where recovery lactate concentration equaled peak exercise concentration acted as the anchor for fitting the line tangent to the blood lactate curve during exercise. The point where the tangent line initially met the blood lactate curve during exercise was taken to represent the individualised anaerobic threshold.

EXERCISE trials were completed during the last 1.5 hours of haemodialysis treatment and included a warm up of five minutes at an intensity equivalent to 50% of the anaerobic threshold. Participants then exercised for 60 minutes at an intensity relating to 90% of their anaerobic threshold. To avoid post exercise hypotension a gradual cool down was carried out until resting blood pressures were reached. A hypotension protocol was also designed and implemented in the case of a hypotensive episode.

TIME trials consisted of an additional 30 minutes added to each patient's current routine haemodialysis time. Thirty minutes was chosen as previous estimations propose that 60 minutes of intradialytic exercise result in urea clearances equivalent to 20 minutes extra dialysis time (Kong *et al.,* 1999). This was expected to improve due to exercise being carried out in the latter half of dialysis. Furthermore, clinicians typically increase dialysis time in 30 minute increments.

Following completion of a diet and medications diary during the three days preceding the first trial, participants were provided with copies of their diaries and asked to maintain a similar dietary and medication intake throughout the study. Trials were carried out during mid and end of week treatment sessions allowing an equal number of non-dialysis days between trials. Haemodialysis treatment parameters were strictly

controlled for including: access type, blood flow, dialysate flow, dialyzer membrane, dialysate concentrate, ultrafiltration rate, temperature, bicarbonate and heparin dosage. The consistency of treatment parameters across trials was checked via trend files downloaded from the haemodialysis machine.

Outcomes.

Solute Clearance. Small molecules urea and creatinine, middle molecule beta$_2$-microglobulin (β_2M) and inorganic substance phosphate were chosen to represent uremic toxins. Blood samples for serum concentrations and pH were taken pre, post and 30 minutes post dialysis according to European Best Practice Guidelines (2002). Pre dialysis samples were taken directly from the dialysis needle immediately before the dialysis hose system had been connected or sodium chloride was injected. Post dialysis samples were taken from the arterial port once the ultrafiltration flow was ceased and blood flow reduced to 100 ml/hr for 15 seconds. These molecules were analyzed at Betsi Cadwaldr University Health Board laboratories using automated analysers (AU2700, Olympus, USA) by individuals blinded to participant identification, trial arm and sample time.

The primary outcome measure was equilibrated Kt/V_{urea} (eKt/V_{urea}) calculated according to European Best Practice Guidelines (2002). This measure was chosen due to its clinical acceptance as a marker of dialysis adequacy. Secondary outcome measures included single pool Kt/V_{urea} ($spKt/V_{urea}$), solute reduction ratios (National kidney Foundation, 2006) and post dialysis rebound of solutes (Kong *et al.,* 1999) [Equations are provided in supplemental materials, pp. 119].

Additionally, continuous sampling of spent dialysate (Argiles *et al.,* 1997; Noiri *et al.,* 2000) using a modified, reverse infusion pump (Perfusor Secura FT, BBraun, Germany) was employed to measure urea, creatinine, β_2M and phosphate excretion in the spent dialysate. Total solute excretion was calculated by multiplying the sample

concentration by the total waste volume (total spent dialysate + ultrafiltration volume). This technique has previously been validated (Argiles *et al.*, 1997; Noiri *et al.*, 2000). In the present study internal validity of this technique was suggested by a significant correlation ($r = 0.71$; $p = 0.007$) with $spKt/V_{urea}$. However, the test - retest coefficient of variation was 37%, suggestive of considerable intraindividual variability of this secondary outcome measure.

Harms. Information on harms was collected actively at the beginning and end of each haemodialysis treatment. Proformas (templates with information completed by a lead researcher following a set pattern) were completed following a participant interview and checking routine haemodialysis treatment records. Specifically, information on musculoskeletal injuries (cramp, muscle soreness, strain or joint pain), cardiovascular events (chest pain or shortness of breath confirmed by an irregular ECG or elevated cardiac markers), episodic hypotension (sudden drop in blood pressure below 90 mgHg or diastolic drop of 20 mmHg with accompanying clinical symptoms) and access complications (altered needle pressures requiring alterations to dialysis pump speed or access site pain) were recorded. Decisions about whether events were attributable to the intervention were made by unblinded clinicians (MMJ, NAJ). The decision whether to withdraw a patient from the trial following a harm was made by discussion between a clinician and the patient.

Other unexpected and serious (fatal, life threatening, or resulted in hospitalisation) harms were collected passively as they occurred and during the trial period only.

Regardless of attribution or withdrawal, all harms are reported.

Statistical Analyses. Where possible the average results of the two haemodialysis sessions of each trial were used for the analyses. However, trials were excluded from analyses if treatment had to be altered or a harm prohibited trial completion. In such a case it was ensured that there was a complete data set from at least one session for each

trial per participant. Trial arms were repeated until one such complete data set was obtained. Thus, in this efficacy study data were analysed and presented on a *per protocol* rather than an *intention to treat* basis.

Following assumption checks, differences in outcome measures between trials were analysed using repeated measures analysis of variance (ANOVA). If the omnibus ANOVA was statistically significant, *post hoc* Tukeys tests were carried out, without adjustment for multiple comparisons, to determine differences between trials. Effect sizes (*d*) were calculated for these *post hoc* comparisons using Cohen's method, and interpreted as small, < 0.3; medium < 0.5; or large, > 0.8 (Cohen, 1988). For the primary outcome measure of eKt/V_{urea} 95% confidence intervals for the difference between the means were also calculated.

Data were analysed using the Statistical Package for the Social Sciences (version 18; IBM, New York, USA). Statistical significance was set at $p \leq 0.05$. Data is presented as mean (SD). Data on harms were presented descriptively only.

Results

Participants. Participant flow through the study is presented in **Figure 4.2.**. Participants' haematology and biochemistry data were within ranges recommended by the Renal Association Standard (Dawnay *et al.*, 2010) (**Table 4.2.**). Exercise intensity at the lactate threshold was 45 (15) Watts.

Treatment Parameters. Complete per protocol data sets from at least one and where possible the average of the two sessions across all trial arms were collected from 11 participants. Eighty-four treatments were carried out in total (26 CONTROL, 33 EXERCISE and 25 TIME). Of these, 58 treatment sessions contributed to the analysis consisting of 22 CONTROL, 19 EXERCISE and 17 TIME trials. Reasons for exclusion of individual trials were CONTROL: 4 access problems; EXERCISE: 3 harms, 8 access problems, 2 haemodialysis machine faults, 1 investigator error; TIME: 2 harms and 6 access problems. Treatment parameters were not significantly different between trials (**Table 4.3.**).

Blood pH increased significantly throughout dialysis, rising from 7.42 (0.01) pre dialysis to 7.47 (0.01) and 7.47 (0.10) at mid dialysis and the end of dialysis, respectively ($p < 0.001$). However, this increase was not different between trials, as evidenced by a non significant main effect for trial ($p = 0.58$) and a non significant time x trial interaction ($p = 0.25$).

Total dialysis time was 237 (9) minutes for CONTROL and EXERCISE trials and 267 (9) minutes for TIME trials. During EXERCISE trials participants cycled for 53 (11) minutes (excluding warm ups, cool down and breaks) at an intensity of 40 (13) Watts.

Equilibrated Kt/V_{urea}. As depicted in **Figure 4.3.** and **Table 4.4.**, TIME significantly increased eKt/V_{urea} in comparison to CONTROL. EXERCISE had no

significant effect on eKt/V_{urea}. The difference and 95% confidence interval between TIME and CONTROL was 0.15 [0.05; 0.26] and between EXERCISE and CONTROL was 0.05 [-0.05; 0.12].

Single Pool Kt/V$_{urea}$. TIME also significantly increased $spKt/V_{urea}$ in comparison to both control and exercise trials (**Table 4.4.**). Exercise had no significant effect on $spKt/V_{urea}$.

Urea. TIME significantly increased serum urea reduction ratio in comparison to both EXERCISE and CONTROL trials (**Table 4.4.**). EXERCISE had no significant effect on serum urea reduction ratio. Although total cleared urea in the spent dialysate showed a similar pattern to serum urea levels, with a higher clearance noted following TIME, values failed to reach statistical significance with small effect sizes observed. Neither TIME nor EXERCISE had any significant effect on the serum urea rebound ratio.

Creatinine. TIME significantly increased the serum creatinine reduction ratio compared to CONTROL trials (**Table 4.4.**). EXERCISE had no significant effect on serum creatinine reduction ratio. Although total cleared creatinine in the spent dialysate showed a similar pattern to serum creatinine levels, with a higher clearance noted following TIME, values failed to reach statistical significance with small effect sizes observed. Neither TIME nor EXERCISE had any significant effect on the serum creatinine rebound ratio.

Beta$_2$-Microglobulin. There was a trend, with a medium to large effect size, towards an increase in serum β_2M reduction ratio following TIME (**Table 4.4.**). EXERCISE had no significant effect on serum β_2M reduction ratios. Although total cleared β_2M in the spent dialysate showed a similar pattern to serum β_2M levels, with a higher clearance noted following TIME, values failed to reach statistical significance

with small effect sizes observed. There were no significant changes in serum β_2M rebound ratios following either TIME or EXERCISE.

Phosphate. In contrast to other uremic toxins, EXERCISE significantly increased the serum phosphate reduction ratio in comparison to CONTROL sessions (**Table 4.4.**). TIME had no significant effect on the serum phosphate reduction ratio. The difference and 95% confidence interval between TIME and CONTROL was 5.0 [-1.0; 11.1] % and between EXERCISE and CONTROL was 8.6 [0.5; 16.7] %. Although total cleared phosphate in the spent dialysate showed a similar pattern to serum phosphate levels (with large effect sizes), with a higher clearance noted following EXERCISE, values failed to reach statistical significance. Neither TIME nor EXERCISE had any significant effect on the serum phosphate rebound ratio.

Harms. Expected harms reported during EXERCISE and TIME sessions were cramp (8/33 [36%] of EXERCISE trials), hypotensive episodes (3/33 [9%] of EXERCISE and 1/25 [4%] of TIME trials) and access problems (4/26 [15%] of CONTROL; 11/33 [33%] of EXERCISE and 6/25 [24%] of TIME trials). One unexpected cardiac event was reported during a TIME trial. Following chest pains confirmed with an irregular ECG the patient was taken off dialysis before the extra dialysis time had commenced and admitted as an inpatient. All harms were resolved without late effects or sequalae.

Discussion

This is the first known study to rigorously compare the effects of intradialytic exercise with that of longer haemodialysis sessions on dialysis adequacy. As expected, an additional 30 minutes of dialysis time was effective at increasing urea and creatinine clearance. There was also a trend towards enhanced β_2M clearance following increased dialysis time. Contrary to what was hypothesised, 60 minutes of aerobic exercise during the last quarter of haemodialysis had no significant effect on dialysis adequacy measured by single pool and equilibrated Kt/V_{urea}. Furthermore, intradialytic exercise did not significantly enhance small or middle molecule clearance measured by creatinine and β_2M clearance, respectively. Intradialytic exercise did, however, show effectiveness at enhancing inorganic phosphate clearance in comparison to routine haemodialysis and additional haemodialysis time.

There appears to be a disparity in the findings of previous studies investigating the effects of intradialytic exercise on dialysis adequacy. The results of the current study contrast with five investigations reporting 15 – 25% increases in dialysis adequacy, as measured by urea clearance, following intradialytic exercise (Kong *et al.,* 1999; Parsons, Toffelmire & King-VanVlack, 2004; Parsons, Toffelmire & King-VanVlack, 2006; Zaluska *et al.*, 2002; Sun *et al.,* 2002). Conversely, the findings of the current study concur with three others demonstrating intradialytic exercise to have no significant effect and small effect sizes on urea clearance (Leung, 2004; Vaithilingam *et al.*, 2004; Adorati, 2000). It was originally hypothesized that these conflicting findings were due to different exercise modes, intensities, durations and timings of exercise during dialysis. Thus the current study implemented an exercise intervention that was physiologically deemed the most effective at enhancing dialysis adequacy. Consequently, the discouraging findings in relation to small and middle molecule clearance, but the positive effect on phosphate removal following exercise warrants

further discussion into the effects of intradialytic exercise prescription parameters on solute clearance.

Previously, simulated equations based on regional blood flow models of dialytic kinetics have suggested that intradialytic exercise would increase urea clearance (Smye, Lindley & Will, 1998). The findings of the current study, however, do not support these equation models as increased blood flow to the muscle tissue induced by exercise hyperemia had no effect on urea clearance.

In addition, these simulated equations further predicted that intradialytic exercise would virtually eliminate urea post dialysis rebound (Smye, Lindley & Will, 1998). Again, the present findings do not reflect this model as exercise hyperemia had no effect on rebound ratios. The reason for the lack of support for the simulated equation model is not immediately clear. Assuming the lack of effect is not due to an issue relating to the study design, presumably the assumptions of the equations are incorrect. One possibility is that the equations are based on the parallel regional blood flow model of urea kinetics, which is a complex model with a large number of assumed parameters (Eloot, Schneditz & Vanholder, 2012). The lack of effect of exercise hyperaemia in the EXERCISE trials as well as the lack of greater rebound ratios despite increased urea clearance with extra dialysis time support this explanation as these effects would be expected according to the parallel regional blood flow model (Schneditz, Platzer & Daugirdas 2009; Schneditz *et al.,* 1995; Schneditz & Daugirdas, 2001).

With regards to β_2M kinetics during dialysis, a classic serial two pool model has been suggested whereby the intercompartmental transfer coefficient appears to be the rate limiting factor of removal (Leypoldt, 2005; Schneditz & Daugirdas, 2001). The flux of this molecule between compartments is relatively slow and does not reach its maximum during a standard haemodialysis session, thus encouraging recommendations for increased dialysis duration rather than more efficient dialysis sessions for enhanced

middle molecule clearance (Leypoldt, 2005). This model *is* supported by the findings of the current study whereby a trend towards increased β_2M clearance was observed following longer dialysis sessions. According to this model, exercise would not be expected to influence β_2M clearance as increased blood flows induced by hyperemia would not increase the intercompartmental transfer rate.

In contrast to longer dialysis sessions, intradialytic exercise significantly enhanced inorganic phosphate reduction ratios. A four pool model has been proposed for intradialytic phosphate kinetics whereby phosphate generation from a third and fourth pool, possibly erythrocytes and bone, occurs when low plasma levels are reached in the later stages of dialysis (Spalding, Chamney & Farrington, 2002). It may be speculatively suggested that during intradialytic exercise the muscle acts as a fifth pool, increasing serum phosphate levels as a result of energy metabolism (Maimoun *et al.*, 2006; Sorlie *et al.*, 1982) with this excess phosphate being cleared by the dialyser. Once exercise is complete, serum phosphate is utilized to replenish muscle stores, explaining lower serum phosphate concentrations observed immediately post dialysis. Clinical benefits include an increased phosphate removal as well as a prevention of additional phosphate release from erythrocytes and bone. The finding that phosphate reduction ratios were increased following exercise and not altered by increased dialysis duration, support suggestions that dialysis efficiency is more effective than increased dialysis duration with regards to phosphate removal (Leypoldt, 2005).

In summary, exercise had no significant effect on dialysis adequacy measured by the primary outcome of urea clearance. Although urea clearance is the preferred clinical marker of dialysis adequacy (National Kidney Foundation, 2006) it has been suggested that the investigation of urea alone may represent an over-simplified view of dialysis adequacy and that dialysis therapy should also aim to increase removal of more toxic middle molecules and inorganic substances (Vanholder *et al.*, 2003; van Wessel *et al.*,

2010). Accordingly, intradialytic exercise did not increase middle molecule clearance but it did result in greater reductions of serum inorganic phosphate. Exercise could therefore be prescribed as an adjunctive therapy for phosphate control (providing cramps and hypotensive episodes are controlled). Furthermore, other studies suggest that exercise provides benefits relating to physical function and cardiovascular health (Cheema, 2008). As exercise did not negatively alter blood pH or increase uremic toxin production in the present study, these findings provide further support that intradialytic exercise should be implemented as part of routine care of haemodialysis patients.

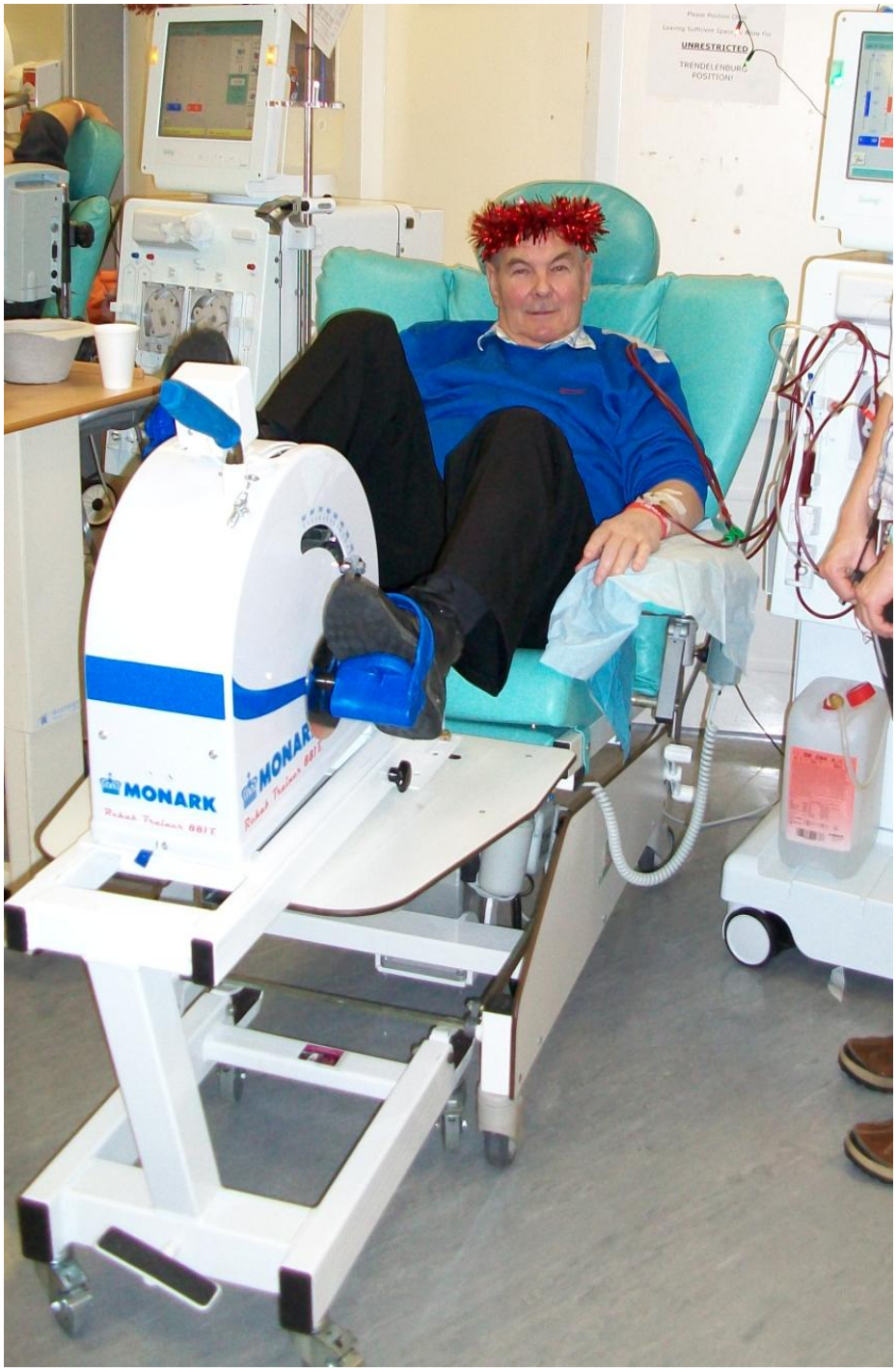

Figure 4.1. A patient participating in the supervised intradialytic cycling required in the EXERCISE arm of the study.

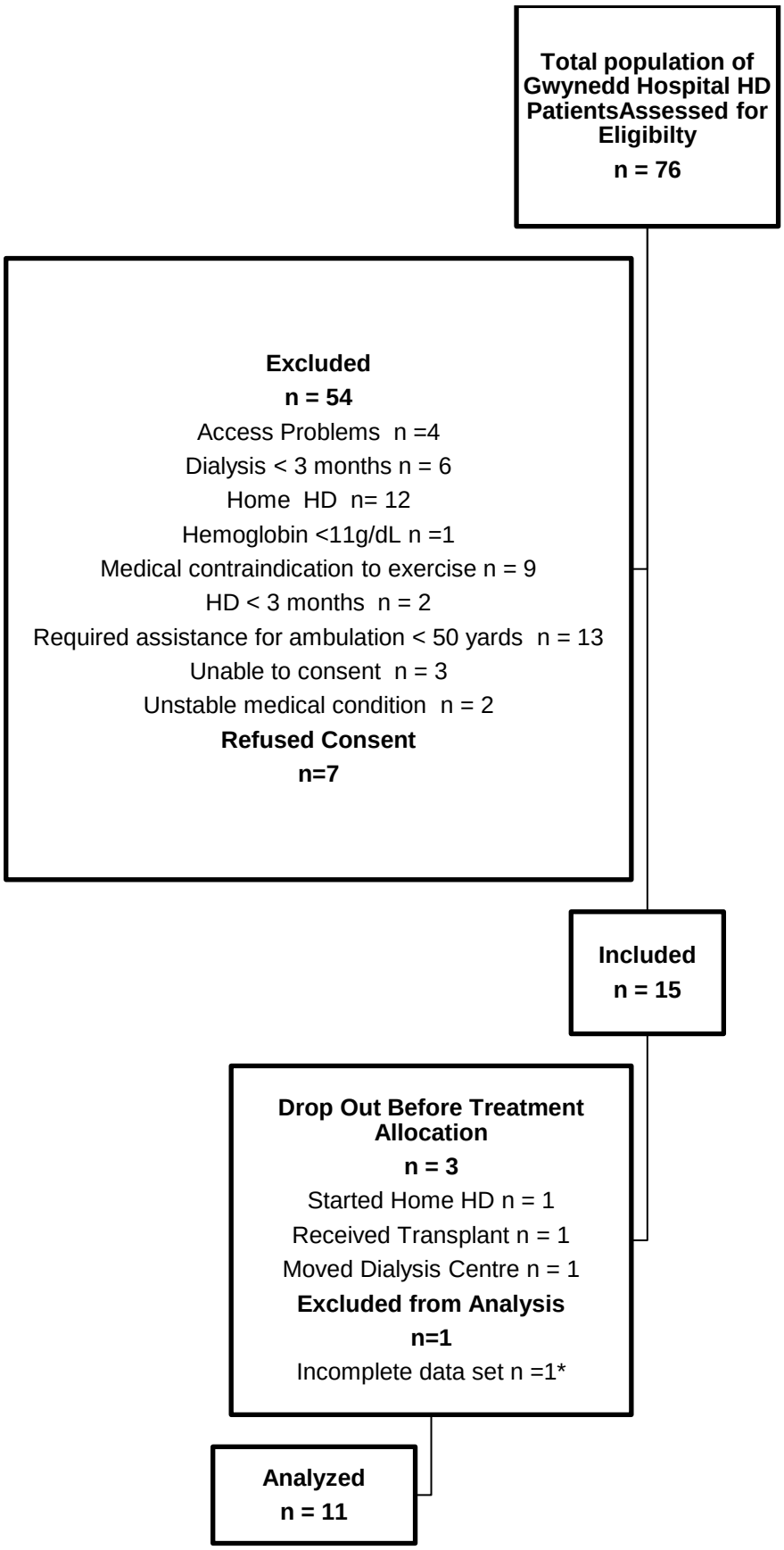

Figure 4.2. Participant flow throughout the study.

*Did not complete exercise trials due to cramp. HD; haemodialysis

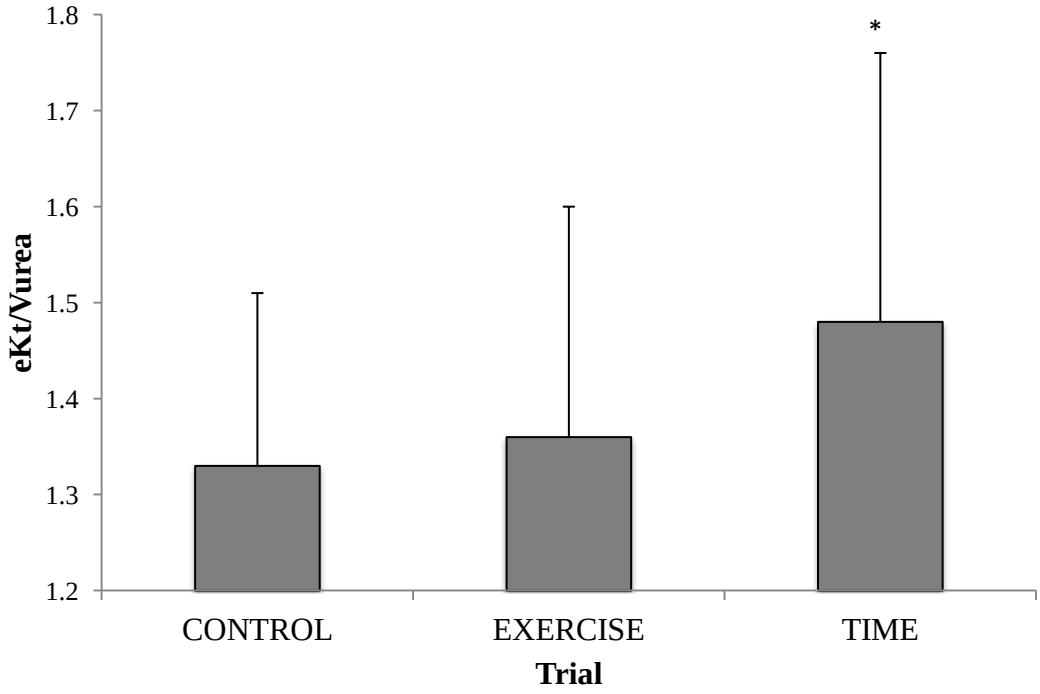

Figure 4.3. Equilibrated Kt/V_{urea} (eKt/V_{urea}) in response to interventions aimed at enhancing dialysis adequacy.

Values are calculated from serum urea concentrations pre, post and 30 minutes post haemodialysis. CONTROL, routine haemodialysis; EXERCISE, cycling exercise carried out during haemodialysis; TIME, haemodialysis time increased by 30 minutes.

Repeated measures analysis of variance showed a significant difference between groups ($p = 0.02$). Post hoc Tukeys tests revealed that increasing haemodialysis time by 30 minutes significantly increased eKt/V_{urea} compared to CONTROL trials ($*p \leq 0.05$) Exercise had no significant effect on eKt/V_{urea} ($p \geq 0.1$)

Table 4.1. Current literature investigating the effects of intradilaytic exercise on solute removal.

Author	Design	Groups	Intervention	Outcome Measure	Difference	Effect Size
Kong (1999) *Nephrol Dial Transplant*	Randomised Crossover	Exercise Control N=11	[A] Aerobic (Cycle) [B] 1 Session [C] 25% increase in HR [D] 60 min (5-20 min bouts) [E] ? [F] N/A	**Urea** Kt/V % Rebound Reduction Ratio Clearance Time **Creatinine** % Rebound Reduction Ratio Clearance Time **Potassium** % Rebound	 ↑ 15% * ↓ 12% * ↑ 7% * ↓ 21% * ↓ 18% * ↑ 11% * ↓29% * ↓ 29% *	Large (2.21)
Adorati (2000) Short Communication *Nephrol Dial Transplant*	Randomised Crossover	Exercise N=8 Control N=?	[A] Aerobic (Cycle) [B] ? [C] Low resistance [D] 80 min (4 X 20 min) [E] Last 20 min x every hour [F] N/A	**Urea** Total Removal (CSSD) % Rebound **Creatinine** Total Removal (CSSD) **Phosphate** Total Removal (CSSD)	 ↑ 2% ↓ 20% [?] ↑ 8% * ↑ 11% *	 Trivial (0.006) Trivial (0.001) Trivial (0.002)

Parsons (2003) *Clin Nephrol*	2 Parallel Groups Randomised Controlled Trial	Exercise N=6 Control N= 7	A Aerobic (Cycle) B 3 x week C 40 –50% max work load D 45 min (3 x 15 min) E 15 min/hr x first 3 hrs F 8 weeks	**Urea**		
				Serum (mmol/l)	↓2% vs. ↑8%	Small/Med (-0.42)
				spKt/V	↔0% vs. ↓4%	Small (0.36)
				eKt/V	↑ 8% vs. ↓3%	Small (0.24)
				Dialysate Clearance (PDS; mmol)	↑ 15% vs. ↓1% *	Large (1.12)
				Creatinine		
				Serum (µmmol/l)	↑5% vs. ↑10%	Trivial (0.04)
				Potassium		
				Serum (mEq/l)	↓0.3 vs. ↑0.1	Large (-1.14)
Vaithilingam (2004) *Am J Kidney Dis*	Randomised Crossover	Exercise Pre Dx Exercise During Dx Control N=12	A Aerobic (Cycle) B 3 x week C ? D 30 – 60 min E ? F 1 week	**Urea**		
				Total Weekly Removal (PDS; g)	↑6%	Trivial (0.01)
				Kt/V	↔ 0%	Nil
				% Reduction	↑2.8	Trivial (0.02)
				Phosphate		
				Serum (mg/dL)	↓ 4%	Trivial (-0.12)
				Total Weekly Removal (PDS; mg)	↑ 9%	Trivial (0.0005)
				Beginning of Week Removal (PDS; mg)	↓ 11%	Trivial (0.001)

Leung (2004) *JESF*	Randomised Crossover	Exercise Control N=15	[A] Aerobic (Cycle) [B] 1 Session (midweek) [C] RPE 3 (moderate) [D] 30 min [E] 120-150 x 240 min [F] N/A	**Urea**		
				Removal (PDS; g)	↑ 6%	Trivial (0.002)
				Rebound (%)	↓2.7%	Trivial (-0.01)
Parsons (2006) *Arch Phys Med Rehabil*	1 Group Repeated Measures	Exercise N=13	[A] Aerobic (Cycle/ Ministepper) [B] 3 x week [C] ↑ HR x 20bpm [D] 60 min (2x 30 min) [E] 0 – 120 min [F] 20 weeks	**Urea**		
				Serum (mmol/l)	↔ 0%	Nil
				spKt/V	↑ 15% *	Large (3.52)
				Creatinine		
				Serum (µmmol/l)	↓ 3%	Trivial (-0.0007)
				Potassium		
				Serum (mmol/l)	↔ 0%	Nil

Percentage difference represents the difference between exercise and control sessions/groups.

spKt/V, single pooled Kt/V; eKt/V, equilibrated Kt/V; dx, dialysis; CSSD, continuous sampling of spent dialysate; PDS, partial dialysate sampling; A, exercise modality; B, exercise frequency; C, exercise intensity; D, exercise duration; E, exercise time during dialysis; F, length of exercise intervention; *, statistical significance declared ($p < 0.05$); ?, information not provided in paper.

Table 4.2. Participant characteristics of analysed data sets.

Demographics	
Age (years)	56 (13)
Gender (male/female)	8/3
BMI (kg/m^2)	28 (7)
Aetiology of CKD (n):	
Arteriopathic	1
Congenital	1
Glomerulonephritis	4
Miscellaneous	5
Co-morbid conditions (n):	
Diabetes	2
Ischemic heart disease	1
Hypertension	6
Medication (tablets/day)	11 (7)
Haemodialysis Characteristics	
Access type (n):	
Arteriovenous fistula	9
Venous catheter	2
Haemodialysis vintage (months)	21 (15)
Haemodialysis duration (minutes)	237 (9)
Blood flow rate (ml/min)	354 (33)
Dialysate flow rate (ml/min)	727 (45)
Dialyzer membrane flux (n):	
High	10
Low	1
Dialysate concentrate (n):	
284 (K 1; Ca 1)	4
375 (K 1; Ca 1.25)	6
380 (K 2; Ca 1.5)	1
Haematology and Biochemistry	
Albumin (g/L)	40 (4)
Pre dialysis β_2M (mg/dL)	25.9 (12.2)
Pre dialysis creatinine (umol/L)	253 (88)
Haemoglobin (g/dL)	11 (0.8)
Pre dialysis phosphate (mmol/L)	1.6 (0.6)
Pre dialysis urea (mmol/L)	16.4 (4.3)

BMI, body mass index; CKD, chronic kidney disease; K, potassium (mmol/L); Ca, calcium (mmol/L); β_2M, beta-$_2$ microglobulin. Data are means (SD) unless stated.

Table 4.3. Haemodialysis treatment parameters across control, intradialytic exercise and increased time trial arms.

Treatment Parameters	Trial			*p*
	CONTROL	EXERCISE	TIME	
Blood flow rate (ml/min)	355 (35)	355 (35)	355 (35)	1.00
Dialysate flow rate (ml/min)	722 (51)	725 (43)	727 (46)	0.39
Arterial pressure (mm/Hg)	-156 (18)	-147 (11)	-146 (19)	0.31
Venous pressure (mm/Hg)	167 (14)	163 (16)	162 (16)	0.27
Transmembrane pressure (mm/Hg)	21 (7)	23 (4)	19 (4)	0.06
UF rate (ml/hr)	466 (254)	425 (231)	415 (221)	0.10
UF volume (ml)	1892 (971)	2315 (2257)	1921 (1029)	0.56

CONTROL, routine haemodialysis; EXERCISE, cycling exercise carried out during haemodialysis; TIME, haemodialysis time increased by 30 minutes. UF, ultrafiltration. Data are means (SD). Statistical significance was determined by repeated measures analysis of variance.

Table 4.4. Uremic toxin solute clearance for interventions aimed at increasing dialysis adequacy.

Measure	Trial			*p*	Effect size (*d*) EXERCISE *vs.* CONTROL	Effect size (*d*) TIME *vs.* CONTROL
	CONTROL	EXERCISE	TIME			
Urea						
Equilibrated Kt/V_{urea}	1.33 (0.18)	1.36 (0.24)	1.48 (0.28)*	0.02	Small	Large
Single pool Kt/V_{urea}	1.51 (0.19)	1.54 (0.24)	1.73 (0.27)*§	<0.001	Small	Large
Urea reduction ratio (%)	73 (4)	74 (5)	77 (5)*§	<0.001	Small	Large
Dialysate urea content (mmol)	284 (126)	288 (131)	302 (165)	0.96	Small	Small
Urea rebound ratio (%)	6 (2)	5 (3)	6 (4)	0.52	Small	Medium
Creatinine						
Creatinine reduction ratio (%)	66 (5)	67 (6)	69 (6)*	0.02	Small	Medium
Dialysate creatinine content (umol)	4525 (4852)	4553 (4725)	4586 (3926)	1.00	Small	Small
Creatinine rebound ratio (%)	10 (4)	10 (4)	9 (3)	0.88	Small	Small
ß$_2$M						
ß$_2$M reduction ratio (%)	50 (10)	53 (7)	58 (11)	0.09	Small	Large
Dialysate ß$_2$M content (mg/dL)	140 (82)	153 (83)	167 (100)	0.13	Small	Small
ß$_2$M rebound ratio (%)	16 (10)	11 (6)	11 (4)	0.12	Medium	Medium
Phosphate						
Phosphate reduction ratio (%)	50 (17)	59 (10)*	55 (12)	0.03	Medium	Small
Dialysate phosphate content (mmol)	22 (6)	28 (18)	27 (16)	0.52	Large	Medium
Phosphate rebound ratio (%)	26 (19)	20 (12)	29 (28)	0.45	Medium	Small

CONTROL, routine haemodialysis; EXERCISE, cycling exercise carried out during haemodialysis; TIME, haemodialysis time increased by 30 minutes; ANOVA, analysis of variance; *, significantly different to control trial ($p < 0.05$); §, significantly different to exercise trial ($p < 0.05$). Effect sizes were calculated and interpreted as small, < 0.3; medium,< 0.5 or large, > 0.8. ß$_2$M, beta$_2$-microglobulin. Statistical significance was determined by repeated measures analysis of variance.

Supplemental Material

Equilibrated Kt/V_{urea} (eKt/V_{urea}):

$$\mathbf{eKt/V_{urea} = -Ln(C_{t30}/C_0 - 0.0083 \times T) + (4 - 3.5 \times C_{t30}/C_0) \times dBW/BW}$$

Whereby $\mathbf{C_0}$, pre dialysis blood urea nitrogen; $\mathbf{C_{t30}}$, 30 minute post dialysis blood urea nitrogen; **T**, dialysis time; **dBW**, body weight loss during dialysis (kg); **BW**, post dialysis weight (kg) (European Best Practice Guidelines 2002).

Single pool Kt/V_{urea} ($spKt/V_{urea}$):

$$\mathbf{spKt/V_{urea} = -Ln(C_t/C_0 - 0.0083 \times T) + (4 - 3.5 \times C_t/C_0) \times dBW/BW}$$

Whereby $\mathbf{C_0}$, pre dialysis blood urea nitrogen; $\mathbf{C_t}$, post dialysis blood urea nitrogen; **T**, dialysis time; **dBW**, body weight loss during dialysis (kg); **BW**, post dialysis weight (kg) (European Best Practice Guidelines 2002).

Reduction Ratios (%):

$$\mathbf{RR = 100 \times ((X_0 - X_t)/ X_0)}$$

Whereby $\mathbf{X_0}$, pre dialysis concentration; $\mathbf{X_t}$, post dialysis concentration. (European Best Practice Guidelines 2002).

Rebound Ratios (%):

$$\mathbf{Rebound = 100 \times ((X_{t30}/X_0)/ (X_0/X_t))}$$

Whereby $\mathbf{X_0}$, pre dialysis concentration; $\mathbf{X_t}$, post dialysis concentration (Kong *et al.*, 1999)

CHAPTER 5

Anabolic Exercise in Haemodialysis Patients: A Randomised Controlled Trial

Source of funding: This study was supported by unrestricted grants from the North West Wales National Health Service Trust Endowment Fund and by North Wales National Health Service Trust Research and Development-Central Area.

Abstract

Background. The anabolic response to progressive resistance exercise training (PRET) in haemodialysis patients remains unclear. This efficacy study aimed to determine whether a novel intradialytic PRET technique could safely reverse atrophy and consequently improve muscle strength and physical function in haemodialysis patients. A second aim was to compare any anabolic response to that of healthy participants completing the same programme.

Methods. In a single blind controlled study, 23 haemodialysis patients and 9 healthy individuals were recruited and randomly allocated to PRET or an attention control (SHAM) group. PRET completed high intensity exercise: leg extensions using novel equipment. SHAM completed low intensity exercise: lower body stretching activities using ultra light latex bands. Exercises were completed thrice weekly, during dialysis in the haemodialysis patients, over 12 weeks. Outcomes included knee extensor muscle volume by magnetic resonance imaging, knee extensor strength by isometric dynamometer, lower body tests of functional capacity, and harms. Data were analyzed by a *per protocol* method using analysis of variance (ANOVA).

Results*:* PRET elicited an anabolic response in both haemodialysis patients (PRET: +84 (123) cm^3; SHAM: -109 (118) cm^3) and healthy participants (PRET: +136 (163) cm^3; SHAM: -32 (54) cm^3) (omnibus ANOVA: p=0.01). PRET also increased knee extensor strength in both haemodialysis patients and healthy participants. In contrast, PRET only enhanced lower body functional capacity in the healthy participants. Harms possibly related to PRET included one case of muscle soreness, and five cases of intradialytic hypotension.

Conclusions*:* Intradialytic PRET elicited a normal anabolic and strength response in haemodialysis patients. The lack of a change in functional capacity was surprising and warrants further investigation. *Registered as a clinical trial: NCT0100783.*

Introduction

Disease and disuse can disturb the normal balance between protein synthesis and breakdown, leading to muscle wasting. Muscle atrophy is frequently observed in maintenance haemodialysis (HD) patients (Workeneh & Mitch, 2010), with 18 – 80% of patients showing evidence of wasting (Mak *et al.,* 2011) via various methods of body composition analysis (Johansen *et al.,* 2003; Macdonald *et al.,* 2004; Sakkas *et al.,* 2003a).

Muscle wasting in this population is an important problem because it is an independent predictor of morbidity and mortality (Huang *et al.,* 2010). Medium to strong positive correlations have also been revealed between muscle quantity and strength, oxygen extraction at the muscle and functional capacity in HD patients (Johansen *et al.,* 2003; Macdonald *et al.,* 2004; Cheema *et al.,* 2010; Marrades *et al.,* 1996), suggesting muscle wasting also reduces physical functioning and habitual daily activity. Thus muscle wasting indirectly affects quality of life (QoL).

Although many causes of muscle wasting have been identified in HD patients, disuse atrophy remains a consistently cited mechanism (Mak *et al.,* 2011) that is rarely addressed by standard routine care. Progressive resistance exercise training may be a safe, cost effective, anabolic intervention, having already been implemented in other diseases characterized by muscle wasting (Lemmey *et al.,* 2009; Singh *et al.,* 1999). However, in HD patients, despite having a positive effect on markers of anabolism (Balakrishnan *et al.,* 2010), the effect of progressive resistance exercise training on muscle quantity, as assessed using recommended endpoints in studies on nutritional status in this population (Senior & Maroni, 1999), remains equivocal (**Table 5.1.**).

For example, supervised outpatient progressive resistance exercise training programmes have failed to reverse muscle atrophy in HD patients (Kopple *et al.,* 2007).

In any case, intradialytic programmes are more acceptable to patients, reducing drop out (Konstantinidou *et al.*, 2002). Of previous studies that have implemented intradialytic progressive resistance exercise training, muscle cross sectional area was assessed using gold standard imaging techniques in three studies (Cheema *et al.*, 2007a; Cheema *et al.*, 2007b; Johansen *et al.*, 2006), but only one significantly decreased muscle wasting (Johansen *et al.*, 2006). Two studies have also utilized the dual energy x-ray absorptiometry technique (Johansen *et al.*, 2006; Chen *et al.*, 2010), but only one significantly reversed atrophy.

Thus the anabolic efficiency of progressive resistance exercise training in HD patients has been described as discouraging (Mak *et al.*, 2011). The cause of this lack of anabolic effect is unclear. Suggested reasons include that HD patients present with hypogonadism (Albaaj *et al.*, 2006), insulin resistance (Mak, Cheung & Roberts, 2008) and a perturbed insulin like growth factor/ growth hormone axis (Mak, 2008), all of which are implicated in activating signaling pathways responsible for protein synthesis. Alternatively, previous interventions may simply have lacked the attributes considered necessary to elicit an anabolic response (Kraemer *et al.*, 2002). For example, interventions may have been of insufficient training load and lacked sufficient progression to elicit hypertrophy.

Therefore the aim of this efficacy study was to determine whether a novel intradialytic PRET technique, that allows overload and progression, could safely reverse atrophy and consequently improve muscle strength and physical function in haemodialysis patients. A second aim was to compare any anabolic response to that of healthy participants completing the same programme. It was hypothesized that PRET would result in significant increases in muscle volume, strength and physical function in HD patients as compared to an attention control group, and that this response would be similar to that observed in healthy participants.

Methods

Study Design. This study was a two-centre, single blind, pre test post test, randomised controlled trial registered on clinicaltrials.gov as NCT01007838. Participants were randomly allocated to receive a progressive resistance exercise training intervention (PRET) or a sham exercise attention control intervention (SHAM) using opaque envelopes in a 1:1 manner, stratified by disease state (HD patients or healthy participants), sex and centre.

Participants. All participants provided written informed consent. Ethical approval was provided by Betsi Cadwaladr University Health Board Ethics Committee and Bangor University. HD patients were recruited from two main centre renal units in North Wales, United Kingdom. Eligible patients presented with Stage 5 CKD receiving maintenance HD three times per week. Patients were excluded if they were below 18 years of age; received HD for less than three months; required support for ambulation of less than 50 metres; presented with haemoglobin levels below 11 g/dL; presented with any neuromuscular or catabolic conditions; had received any anabolic treatment in the preceding three months; presented with acute infection; had any uncontrolled medical condition (e.g. poor diabetic control, poor dialysis adequacy); poor dietary control requiring dietician referral (e.g. insufficient protein intake); presented with contraindications to take part in exercise or were unable to provide consent.

Currently sedentary but otherwise healthy participants were recruited via opportunistic sampling from the local North Wales community using posters placed in community centres. Participants were excluded if their general practitioner deemed the participant to have a contraindication to exercise, had suffered from a catabolic condition or received an anabolic or exercise intervention in the preceding three months.

Intervention. The PRET groups completed a 12 week progressive resistance training programme three times per week, during routine HD sessions for the patients and during regular University visits for the healthy participants. Participants were encouraged to eat a light meal two hours before each exercise session.

Each session involved a leg press exercise using specially designed equipment (Fitness Systems, Bolton, UK) designed to fit to the end of a dialysis chair (Stephen H Anatomical New, Gardhen Bilance, Pomigliano d'Arco, Italy) (**Figure 5.1.**). Large training loads were required to allow adequate training progression but obtaining these loads with traditional plate loading machines was deemed as unsafe and impractical in the renal unit. Therefore, the leg press equipment was designed to utilize a series of resistance bands providing a maximum resistance equivalent to 200 kg. In a pilot study the equipment was validated by using a tension load cell (Model 615 S, Tedea Huntleigh, Vishay, Basingstoke, UK), resolved and converted to force in kg by a data acquisition and analysis system (PowerLab 16SP; AD Instruments PTY, Colorado Springs, CO) to determine the resistance of various combinations of the resistance bands throughout the range of movement of the machine. These calculated resistances were used to set and record training intensity.

At the beginning of the programme, the one repetition maximal strength of the participants was predicted from an assessment of their five repetition maximum lift. This method has been validated previously (Brzycki, 1993) and was used to reduce the theoretical risk of injury associated with one repetition maximal strength testing in this population (Painter & Krasnoff, 2002). In training sessions, participants completed a five minute warm up, and then carried out three sets of eight to ten repetitions at 80% of their predicted one repetition maximum with one to two minutes rest period between each set (**Figure 5.2**). Based on resistance exercise biology, this training protocol was deemed to be the most effective at eliciting a hypertrophic response (Kraemer *et al.*,

2002). When 10 - 12 repetitions could be completed at a rating of perceived exertion (RPE) below 15 (hard), predicted one repetition maximum was re-determined and the resistance increased. Weekly training volume was calculated as kg per lift × lifts per session × sessions per week.

The SHAM attention control group carried out a series of unprogressive stretches using an ultra light Thera-Band® (Hygenic Corporation, Akron, Ohio; **Figure 5.2.**). One stretch was carried out per week; stretches were selected from dorsiflexion, plantarfexion, knee flexion, knee extension, hip flexion and leg extension exercises.

Outcomes. Outcome measures were assessed two days before and two days after the first and last intervention session, respectively, using assessors blinded to group allocation. HD patients were assessed following a routine dialysis session and only if clinically determined dry weight targets were achieved.

Thigh Muscle Volume. The primary outcome measure was thigh muscle volume (quadriceps femoris, hamstrings, adductors) determined by magnetic resonance imaging. A three Tesla Philips Achieva magnetic resonance imaging system (Philips Healthcare, Best, The Netherlands) was used to obtain T1 and T2 images in the axial plane from the femoral tibial joint line to the top of the femoral head. The image parameters were as follows: T1 - acquisition matrix of 236 x 236, FOV 475 x 475 x 198, voxel size 2 × 2 mm^2, TE 2.3 ms, TR 4 ms, slice thickness 5 mm, acquisition time 3 minutes. An example of the images obtained is displayed in **Figure 5.3.** The muscle cross sectional area of 12 evenly spaced axial slices (Tracy *et al.*, 2003) was determined by manual tracing using image processing software (Version 4.x, Osirix, Pixmeo, Geneva) run on a laptop (MacBook Pro, OS X 10.6, 2.9 GHz Intel dual core processor with 6 GB ram, Apple, Holyhill, Ireland). The truncated cone formula was applied to calculate muscle volume. The test re-test reliability of this protocol, obtained in five

participants over a period of two days, expressed as a coefficient of variation (CV) was 1.5% with an interclass correlation ($ICC_{3,k}$) of 0.997.

Muscle Strength. Isometric bilateral knee extensor strength was measured using a custom made isometric chair (Bodycare Products, Southam, UK) equipped with a load cell (615 S, Tedea Huntleigh, Vishay, Basingstoke, UK), resolved and converted to force in newtons by a data acquisition and analysis system (PowerLab 16SP; AD Instruments PTY, Colorado Springs, CO). Following a sub-maximal warm up and familiarization trial, three maximal voluntary contractions were performed with a minute rest between each. The highest value was used in the analysis. The $ICC_{3,k}$ of this test has previously been reported as 0.960 (Macdonald *et al.*, 2005).

Physical Function. Physical function was determined using a selection of tests from the Senior Fitness Test (Rikkli & Jones 2001). Physical function tests included the 30 second sit to stand test, a measure of lower body strength ($ICC_{3,k}$ = 0.89); the eight foot get up and go test, a measure of speed and agility ($ICC_{3,k}$ = 0.95) and the six minute walk test, a measure of aerobic capacity ($ICC_{3,k}$ = 0.94) (Rikkli & Jones 2001).

Harms. Information on harms was collected actively at the beginning and end of each exercise session. Proformas (templates with information completed by a researcher following a set pattern) were completed following a participant interview and, in HD patients, by checking routine dialysis treatment records. Specifically, information on musculoskeletal injuries (cramp, muscle soreness, strain or joint pain), cardiovascular events (chest pain or shortness of breath confirmed by electrocardiograph or elevated cardiac markers), acute hypotension (fainting and concomitant low blood pressure), acute hypertension (headache, altered vision, nosebleed or shortness of breath and concomitant high blood pressure) and access complications (altered needle pressures requiring alterations to dialysis pump speed or access site pain) were recorded.

Other unexpected and serious (fatal, life threatening, or resulted in hospitalization) harms were collected passively as they occurred and during the trial period only. Decisions about whether events were attributable to the intervention were made by un-blinded clinicians at each site (MMJ, NAJ and MJK). The decisions whether to withdraw a patient from the trial following a harm was made by discussion between a clinician and the patient. Regardless of attribution or withdrawal, all harms are reported here.

Quality of Life. Although this study was not designed or powered to assess quality of life as a primary outcome, preliminary data on self reported quality of life were obtained using the Short Form-36 version 2 (SF-36v2) health survey questionnaire (Ware *et al.*, 2007). The SF-36v2 consists of 36 items which encompass eight domains of quality of life including physical function, role limitations due to physical health, role limitations due to emotional problems, bodily pain, vitality, general health, emotional well being and social functioning.

Statistical Analysis. Data on harms and compliance were presented descriptively only. Other data were analysed using the Statistical Package for the Social Sciences (version 18; IBM, New York, USA) and presented as mean (SD). Statistical significance was set at $p \leq 0.05$. Absolute data and absolute change data are reported as mean (standard deviation). In this efficacy study data were presented and analysed on a *per protocol* basis.

Training loads in the PRET groups over the twelve week period were compared using a repeated measures analysis of variance with a between group factor of disease state (HD *vs.* healthy) and a within group factor of time (weeks one to twelve).

At first, a between groups analysis of covariance (ANCOVA) was conducted to assess the effectiveness of progressive resistance training in CKD and healthy groups on muscle volume, knee extensor strength, physical function and quality of life. Covariates

were pre test scores for all main outcome measures, taken prior to the administration of any intervention. Dependant variables were post test scores for all main outcome measures. However, the ANCOVA assumption of homogeneity of regression slopes was violated. Therefore, absolute change scores were analyzed via a single factor ANOVA omnibus test with four groups: HD PRET, HD SHAM, healthy PRET and healthy SHAM. If this omnibus ANOVA was significant, comparisons of the response between groups were made by *post hoc* independent *t* tests on change scores without adjustment for multiple comparisons. Thus the response could be compared i) between PRET and SHAM within the HD patients; ii) between PRET and SHAM within the healthy participants; and iii) between HD patients and healthy participants within the PRET group. The mean difference of change scores between groups and 95% confidence intervals were reported for muscle volume, strength and physical function measures. Effect sizes (*d*) were also calculated for these *post hoc* comparisons using Cohen's method, and can be interpreted as small (0.3), medium (0.5) or large (0.8) (Cohen, 1988).

Analyses were completed following assumption checks for parametric, independent, nominal and normally distributed data, as well as homogeneity of variance and sphericity.

Results

Participants, compliance and training volume. The participants' flow through the study is presented in **Figure 5.4.**. Demographic and anthropometric data are presented in **Table 5.2.**. Although there were no statistical differences between the disease groups for age, height, body mass, or body mass index, the patients were slightly (albeit not statistically) older than the healthy participants (54.1 (16.8) vs. 45.0 (16.1) years, $p = 0.2$). All HD patient baseline biochemistry and dialysis data were within Renal Association recommended ranges (**Table 5.2.**) and did not significantly change in either group throughout the study (data not shown). Furthermore no patient's haemoglobin concentration dropped below 11 $g \cdot dL^{-1}$ during the study.

In the PRET groups, training volumes significantly increased over the 12 week intervention period as evidenced by a significant analysis of variance main effect of time ($p = 0.03$, **Figure 5.5.**). An increase in training volume of a similar extent was observed in the healthy participants, shown by a non-significant group x time interaction ($p = 0.3$), and a non-significant main effect of group ($p = 0.2$). Compliance to PRET was similar in both HD patients and healthy participants with 94 (3) % and 93 (3) % of training sessions completed, respectively. Despite the high exercise intensity, all participants were able to complete all 3 sets of 8-10 repetitions throughout the programme. Reasons for missing sessions in the HD PRET group were illness (14 sessions), scheduling issues (2 sessions) and dialysis equipment problems (2 sessions). Reasons for missing sessions in the healthy PRET group were holidays (8 sessions) and unexplained nonattendance (4 sessions).

Thigh Muscle Volume. PRET elicited a significant anabolic response in haemodialysis patients (**Figure 5.6.**; **Table 5.3.**) with a significant increase in muscle volume observed in HD PRET compared to HD SHAM ($p = 0.007$; $d = 0.4$; 95% CI,

193 [63; 324] cm^3). A trend and strong effect size for a greater change in muscle volume was shown in healthy PRET compared to healthy SHAM (p = 0.1; d = 0.2; 95% CI, 169 [-41; 379] cm^3) in response to PRET. There was no significant difference in muscle volume change between HD PRET patients and healthy PRET participants (p = 0.5; d = 0.1) suggesting a similar anabolic response to resistance exercise.

Knee Extensor Strength. PRET elicited a significant strength response in haemodialysis patients (**Figure 5.7.**; **Table 5.3.**) as evidenced by a significantly greater change in HD PRET compared to HD SHAM (p = 0.01; d = 0.6; 95% CI, 56 [15; 98] N). A trend and strong effect size for a greater change in healthy PRET compared to healthy SHAM (p = 0.06; d = 1.0; 95% CI, 118 [-9; 245] N) was shown (**Figure 5.7.**; **Table 5.3.**). There was no difference in knee extensor strength between HD PRET patients and healthy PRET participants (p = 0.6; d = 0.2) suggesting a similar strength response to resistance exercise between HD and healthy participants.

Physical Function. PRET only elicited an improvement in physical functioning in healthy participants. For sit to stand scores, a significant omnibus ANOVA (p = 0.003; **Table 5.3.**) was followed up and revealed a significantly greater change in healthy PRET compared to healthy SHAM (p = 0.005; d = 0.2; 95% CI, 5 [3; 8] units). In contrast, in the HD patients the response to PRET was not different to SHAM (p = 0.3; d = 0.3; 95% CI, 1 [-1; 4] units). Furthermore, the response to PRET was greater in the healthy participants than in the HD patients (p = 0.004; d = 0.8).

Similarly, *f*or six minute walk distance, a significant omnibus ANOVA (p = 0.03; **Table 5.3.**) was followed up and revealed a significantly greater change in healthy PRET compared to healthy SHAM (p=0.01; d = 3.03; 95% CI, 31[36; 188] yards). In contrast, in the HD patients the response to PRET was not different to SHAM (p = 0.4; d = -0.17; 95% CI, 15 [-25; 54] yards). Combined with the finding that the response to PRET was similar in the healthy participants and the HD patients (p = 0.7, d = 0.32) the

data suggest that PRET enhances six minute walk distance, but in HD patients this enhancement is no greater than SHAM exercise.

For eight foot get up and go scores the omnibus ANOVA was not significant (p = 0.3; **Table 5.3.**) and therefore was not followed up. Thus the data reveal that regardless of disease state PRET is no more effective than SHAM exercise at improving eight foot get up and go scores.

Harms. In HD patients expected harms reported in the PRET and SHAM groups, respectively, were musculoskeletal (cramp: 5 vs. 5; delayed onset of muscle soreness: 1 vs. 0; joint pains: 0 vs. 5) and hypotension (5 vs. 0). An unexpected reported harm was laceration wounds on the back (PRET: 1; SHAM: 0). In the healthy participants, only one musculoskeletal harm was reported (delayed onset of muscle soreness), and this was in the PRET group.

Quality of Life. In the domains of bodily pain and social functioning, PRET generally had a positive effect in the healthy participants but this was not the case in the HD patients. Specifically, PRET elicited a large and significant improvement in bodily pain in healthy participants (omnibus ANOVA: p = 0.003; PRET: +34 (5) %; SHAM: -3 (16) %; p = 0.005; d = 2.4) but not in HD patients (PRET: 0 (15) %; SHAM: +2 (15) %; p = 0.1; d = 0.1). PRET also elicited a large and significant improvement in social functioning in the healthy participants (omnibus ANOVA: p =0.04; PRET: +23 (20) %; SHAM: -9 (19) %; p = 0.05; d = 1.4) but not in HD patients (PRET: +7 (18) %; SHAM: -1.5 (8) %; p = 0.2; d = 0.3). Progressive resistance training had no significant effects on change scores for physical function (omnibus ANOVA: p = 0.1), role limitation due to physical problems (omnibus ANOVA: p = 0.5), general health (omnibus ANOVA: p = 0.3), vitality (omnibus ANOVA: p = 0.4) and role limitation due to emotional problems (omnibus ANOVA: p = 0.4) in either the healthy participants or HD patients.

Discussion

In an attempt to determine if muscle wasting could be reversed in HD patients, the aim of this single blind randomized controlled trial was to implement an intradialytic exercise programme that met basic progressive resistance exercise training principles. As hypothesized, using novel equipment that allowed adequate overload and progression, twelve weeks of high intensity PRET elicited an anabolic response in HD patients and healthy participants. PRET also increased muscle strength. However, an unexpected finding was that in HD patients PRET was no more effective than SHAM exercise at improving functional capacity.

When the temporal nature of muscle wasting observed herein in the HD SHAM group (and previously by other authors (Johansen *et al.,* 2003; Johansen *et al.,* 2006)) is taken into account, the anabolic response to PRET in HD patients appears to be normal. In the present study there is exactly a 6% difference in response of muscle volume between PRET and SHAM interventions, in both the HD patients and the healthy participants. These data are somewhat in contrast to the majority of previous studies (Kopple *et al.,* 2007; Cheema *et al.,* 2007a; Cheema *et al.,* 2007b; Castaneda *et al.,* 2001) and a recent meta-analysis (Heiwe & Jacobson, 2011) that have failed to show a significant hypertrophic response to exercise in HD populations. The simplest explanation is that previous studies have not provided significant overload and progression; resistance training guidelines state that adaptation processes will only occur if a greater force is continually exerted to meet higher physiological demands (Kraemer *et al.,* 2002). It is doubtful that this simple principle has been adhered to in previous studies that have prescribed intradialytic exercise utilising ankle weights that can only provide a maximum weight of 15 kg.

It should also be remembered that the anabolic response observed herein is supported by two previous studies (Johansen *et al.*, 2006; Chen *et al.*, 2010). In fact, in those studies' the anabolic response was slightly larger (8-10%) than observed herein, perhaps because the present study utilized only one lower body exercise, where as previous studies have utilized multiple lower and whole body exercises that might be expected to induce a larger and systemic hypertrophic effect (Dong & Ikizler, 2009). Furthermore, in the present study the use of an attention control group rather than just routine care, and an outcome of whole thigh muscle volume rather than muscle cross sectional area, may reduce the size of the reported anabolic response.

Encouragingly, these findings suggest that if anabolic resistance is present in HD patients (Mak *et al.*, 2011), this resistance can be overcome providing exercise programmes are of sufficient training volume. Thus despite perturbed sex hormone, insulin and insulin like growth factor/growth hormone pathways (Mak *et al.*, 2011, Albaaj *et al.*, 2006), an anabolic response to PRET is possible in HD patients. This finding is consistent with studies that have administered sex hormones (Johansen *et al.*, 2006) and insulin-like growth factor/growth hormone (Storer 2009), successfully increasing muscle volume.

Interestingly, the response of functional capacity to PRET differed between HD and healthy participants. Although increases in strength in the HD patients following PRET appeared promising, they did not translate into improved sit to stand, get up and go or six minute walk test scores. In fact this disappointing finding is consistently reported in studies investigating intradialytic progressive resistance training in HD patients (Cheema *et al.*, 2007a; Cheema *et al.*, 2007b; Johansen *et al.*, 2006; Chen *et al.*, 2010). This lack of an effect is particularly surprising, considering similar interventions carried out in other catabolic conditions (such as rheumatoid arthritis) have shown significant increases in the same measures of functional capacity as utilized in the

present study (Lemmey *et al.,* 2009). It is noteworthy that for six minute walk test data, PRET and SHAM exercise similarly increased functional capacity; it is possible that despite familiarization with outcome measures, patients could have felt apprehensive and been over cautious in the baseline tests, resulting in a learning effect in both groups at post test. Variability in this learning effect may have masked any potential interactions (Hopkins, 2000). However, it is also interesting to note that intradialytic aerobic exercise has generally proven successful at enhancing functional capacity in HD patients (Macdonald *et al.,* 2005; Cheema *et al.,* 2006). Speculatively, intradialytic PRET may be compromised due to the difficulty of completing exercising on a dialysis chair, restricting movement throughout the range of motion required to improve functional capacity. Medication use or comorbidities in this population may also blunt the expected functional response to PRET. Future research in this area could provide an interesting insight into the mechanisms behind enhanced functional capacity in this population.

Progressive resistance exercise training also had no effect on QoL in HD patients. Assuming this was not due to being underpowered to detect changes in QoL, a possible explanation could be that patients who volunteer to take part in exercise trials are generally healthier patients with a better quality of life. In fact, the patients who took part in this study presented with QoL scores similar to age matched Welsh normative values of healthy individuals (Burholt & Nash, 2011). In addition, exclusion criteria meant that patients with uncontrolled medical complications, and therefore an expected poorer QoL, were excluded from this study. It is possible that had these patients been included they may have experienced greater QoL changes as a result of an exercise intervention.

A limitation to this study was the absence of whole body protein synthesis and diet measurements to indicate whether nutritional intake confounded body composition

responses. Previous literature has shown large increases in body fat percentage following PRET (Johansen *et al.*, 2006; Headley *et al.*, 2008), perhaps due to an increased appetite following exercise (Hopkins *et al.*, 2011). In addition protein intake may moderate anabolism in response to muscle contraction (Burd, Wall & van Loon, 2012). A further limitation lies in the small, conveniently sampled healthy control group. As a result, it is stressed that statistical comparisons between diseased and non-diseased participants' response to PRET should be interpreted cautiously. However, the strength of including this comparison group is that it allows, for the first time, such comparisons to be made.

In conclusion, using novel intradialytic equipment to allow adequate overload, PRET was safe, and increased muscle volume and strength in hemodialysis patients. A similar anabolic response to PRET was observed in HD patients and healthy participants, precluding assumptions of anabolic resistance to exercise in this patient population. However, the clinical significance of an increase in muscle volume by 6% (as observed herein) remains to be determined. While reversing muscle wasting is theoretically beneficial for reducing morbidity and mortality, the lack of an effect on functional capacity and quality of life was surprising and warrants further investigation.

Figure 5.1. Novel resistance exercise equipment (Fitness Systems, Bolton, UK) designed equipment designed to fit to the end of a dialysis chair (Stephen H Anatomical New, Gardhen Bilance, Pomigliano d'Arco, Italy). The leg press equipment utilised a series of resistance bands providing a maximum resistance equivalent to 200 kg.

Figure 5.2. Haemodialysis patients, allocated to the SHAM attention control group (left) and the PRET group (right), participating in their respective interventions during a routine haemodialysis session**.**

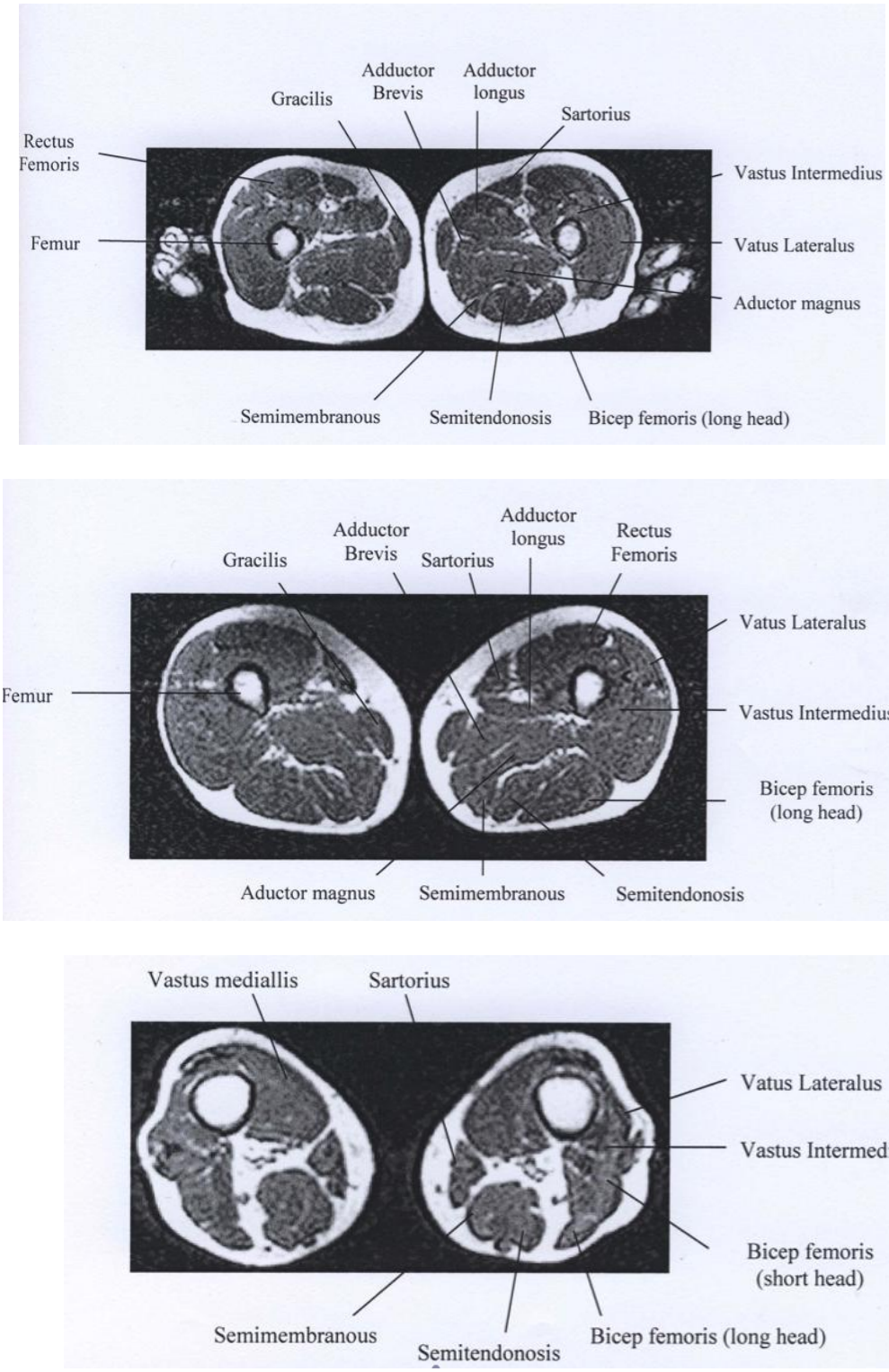

Figure 5.3. Example of a cross sectional T1 weighted magnetic resonance imaging scan of the thigh muscles. Slices are taken from 30% (top), 50% (middle), and 80% (bottom) of the length of the thigh as measured from the top of the femoral head to the femoral tibial joint line.

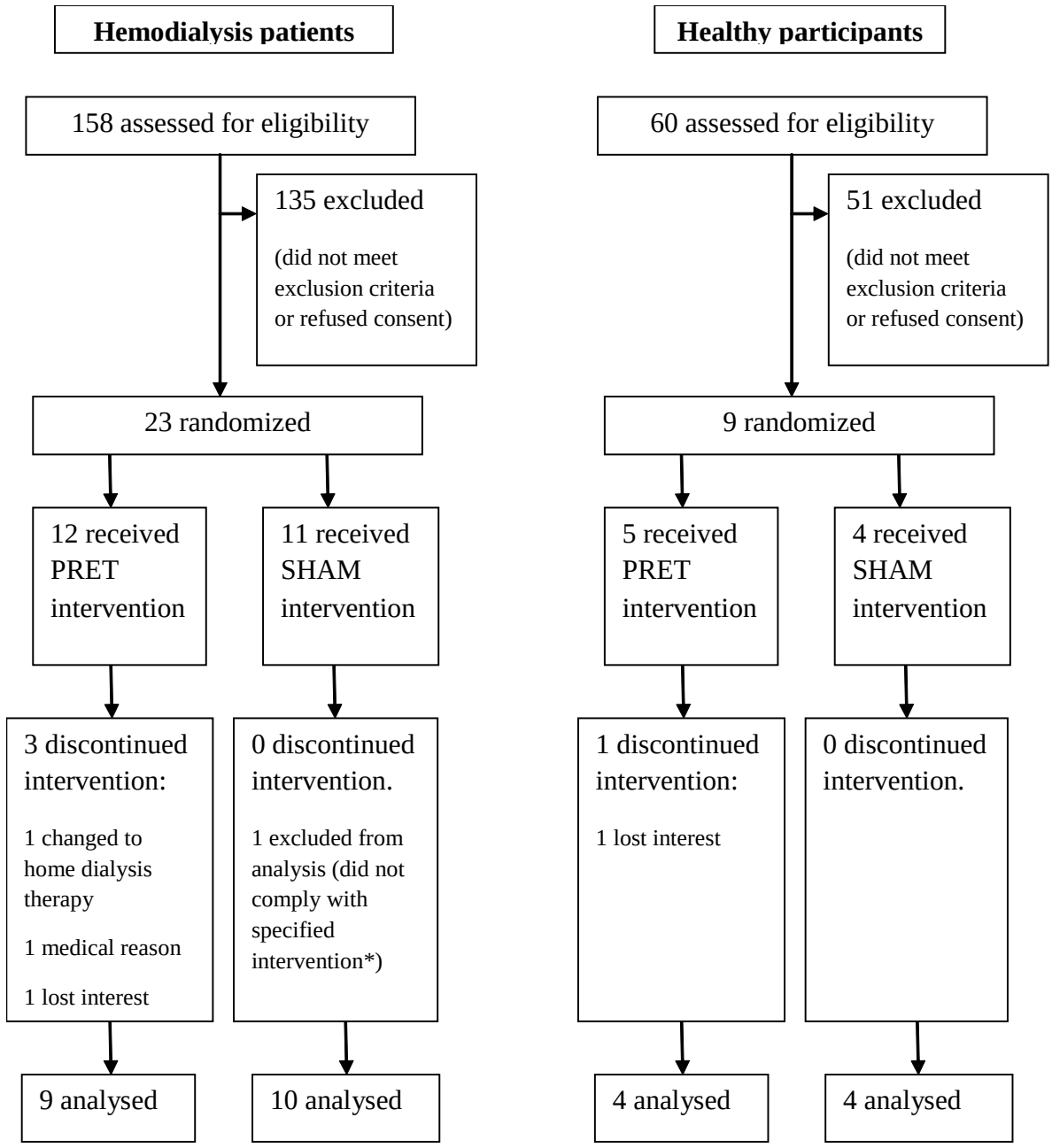

Figure 5.4. Participant flow throughout the study.

PRET, progressive resistance exercise training; SHAM, attention control.

*, completed additional exercise.

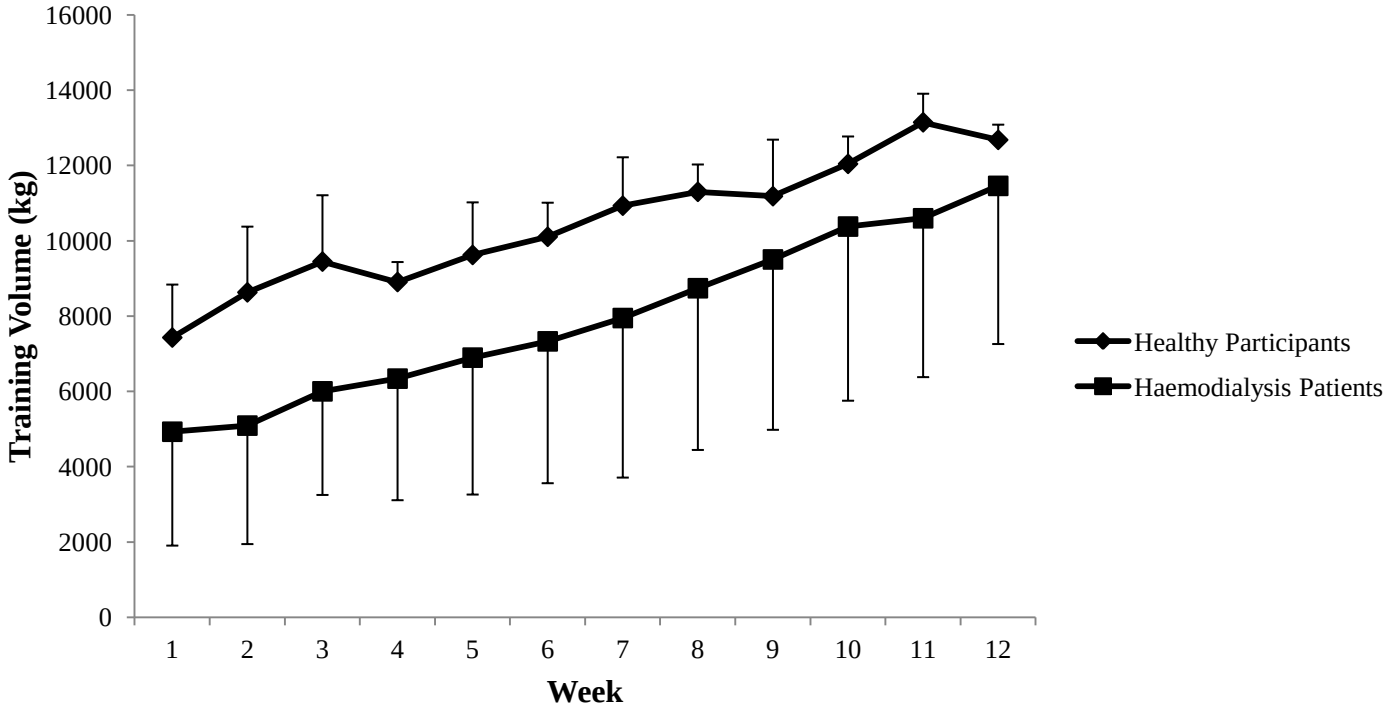

Figure 5.5. Training volume in progressive resistance exercise training groups over the 12 week intervention period.

Training volume increased from week one to twelve similarly in both haemodialysis patients and healthy controls, as evidenced by a significant main effect of time by analysis of variance ($p = 0.03$), a non-significant group x time interaction ($p = 0.3$) and a non-significant main effect of group ($p = 0.2$).

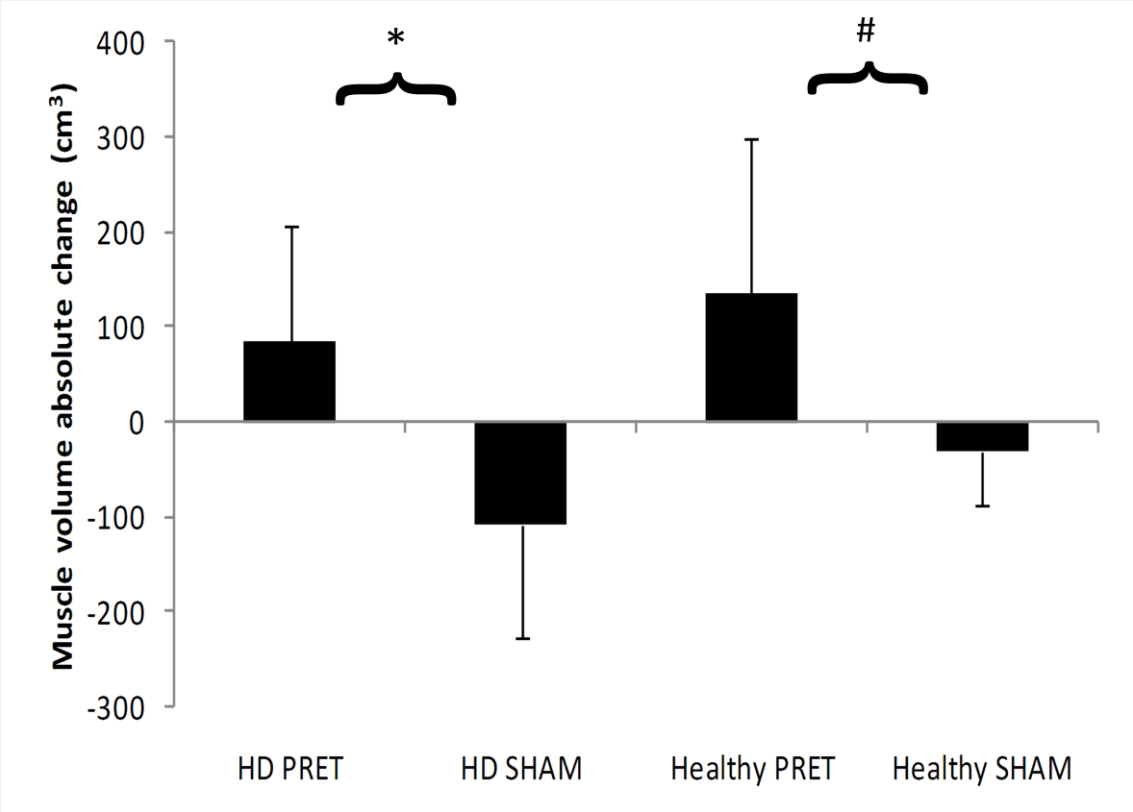

Figure 5.6. Changes in absolute thigh muscle volume by magnetic resonance imaging over the 12 week intervention period

HD, haemodialysis patients; PRET, progressive resistance exercise training; SHAM, attention control. PRET elicited anabolic responses in haemodialysis patients and healthy participants, as evidenced by a significant omnibus analysis of variance ($p = 0.01$), and *post hoc* independent *t*-tests between PRET and SHAM groups (*, $p < 0.05$; #, $p < 0.10$).

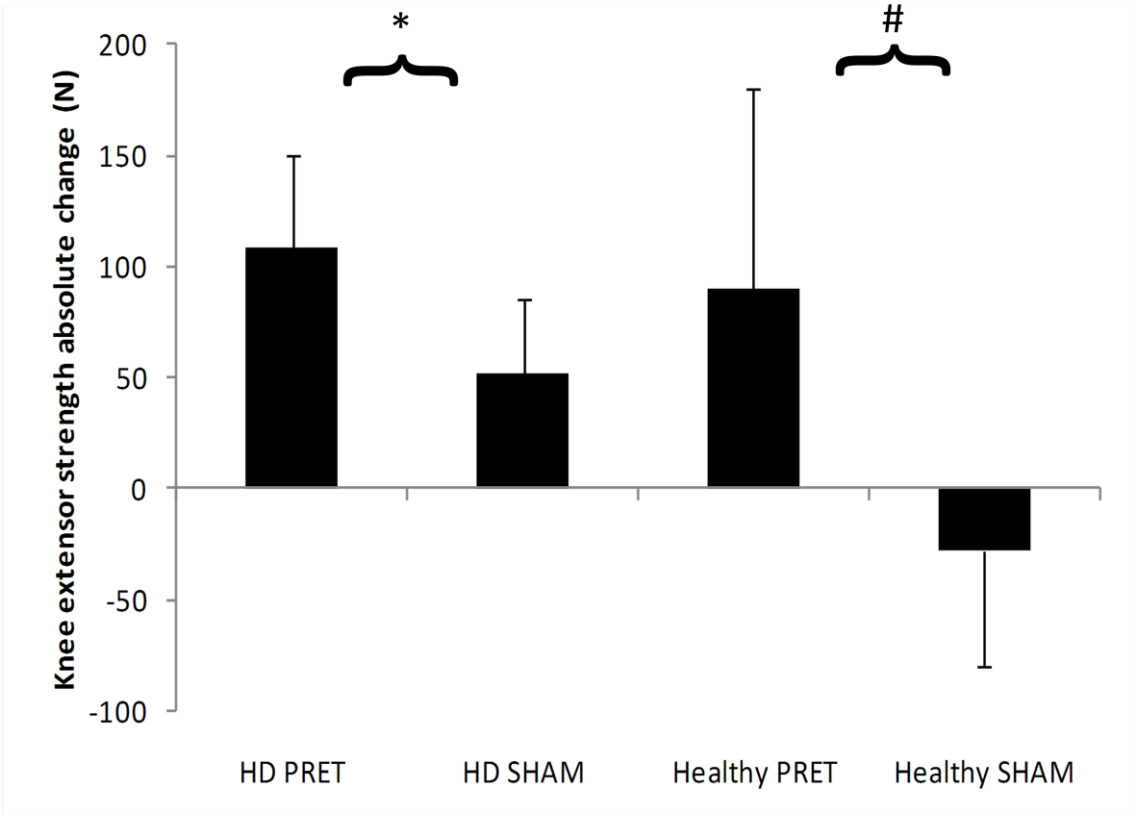

Figure 5.7. Isometric knee extensor strength absolute change over the 12 week intervention period. HD, hemodialysis patients; PRET, progressive resistance exercise training.

PRET elicited a strength response in hemodialysis patients and healthy participants, as evidenced by a significant omnibus analysis of variance ($p = 0.002$), and *post hoc* independent *t*-tests between PRET and SHAM groups (*, $p < 0.05$; #, $p < 0.10$).

Table 5.1. Current literature investigating the effects of resistance training on body composition measures of recommended nutritional endpoints in CKD patients.

First Author	Design	Groups	Intervention	Outcome Measure	Results	Effect Size
Intradialytic Studies						
Chen (2010) *Nephrol Dial Tranplant*	RCT	• Resistance Exercise • Control	[A] Lower body PRT using ankle weights [B] 2 x Week [C] 60% 1RM (6-10 RPE) [D] 2 sets x 8 reps [E] 12 Weeks	**DXA** Whole Body Lean Mass (kg) Leg Lean Mass (kg) Whole Body Fat Mass (kg)	Exercise: ⇑ 5%* Control: ⇓ 3% Exercise: ⇑ 4%* Control: ⇓ 4% Exercise: ⇓ 5%* Control: ⇑ 7%	Small/ Medium (0.4) Small (0.33) Small (0.36)
Cheema (2007) *Am J Kidney Dis*	RCT	• 12 Week Resistance Exercise • 24 Week Resistance Exercise	[A] Whole body PRT using free and ankle weights [B] 3 x Week [C] RPE 15 - 17 [D] 2 sets x 8 reps [E] 12 Weeks	**CT** Thigh Muscle CSA (cm^2) Intramuscular Fat	Exercise: ⇑ 2 % Exercise:⇑0.2 %	Medium (0.59) Very Small (0.07)
Cheema (2007) *JASN*	RCT	• Resistance Exercise • Control	[A] Whole body PRT using free and ankle weights [B] 3 x Week [C] RPE 15 - 17 [D] 2 sets x 8 reps [E] 12 Weeks	**CT** Thigh Muscle CSA (cm Thigh Muscle Attenuation (Hounsfield Units) Total Mid Thigh Fat (cm^2)	Exercise: ⇑ 1 % Control: ⇓0.9 % Exercise: ⇑ 1 Control: ⇓0.9 % Exercise:⇓0.1 % Control: ⇓0.5 %	Small (0.3) Medium (0.52) Very Small (0.02)

Johansen (2006) *JASN*	RCT	• Resistance Exercise • Control • (Nandrolone Decanoate) • (Nandrolone Decanoate + Exercise)	[A] Lower body PRT using ankle weights [B] 3 x Week [C] 60% 3RM [D] 3 sets x 8 reps [E] 12 Weeks	**DXA** Lean Body Mass (kg) Fat Mass (kg) **MRI** Quadriceps CSA	Exercise: ⇑2 % Control: ⇓ 0 % Exercise: ⇑9 %* Control: ⇑0.4 % Exercise: ⇑3 %* Control: ⇓7 %	Very Small (0.18) Very Small (0.16) Medium (0.4)
Supervised Outpatient Studies						
Kopple (2007) *JASN*	RCT	• Resistance Exercise • Control • (Aerobic Exercise) • (Resistance + Aerobic Exercise)	[A] Lower body PRT using weight machines [B] 3 x Week [C] 70-80% 5RM [D] 3 sets x 8 reps [E] 18 Weeks	**Anthropometry** Mid Thigh Muscle Area (cm^2) **DXA** Fat free Mass (kg) Leg Fat Free Mass (kg)	Exercise: ⇑3 % Control: ⇑ 1 % Exercise: ⇑1 % Control: ⇑ 2 % Exercise: ⇑2 % Control: ⇑ 1 %	Medium (0.4) Very weak (0.1) Very Weak (0.06)
Headley (2002) *Am J Kidney Disease*	Within Subject	• Control • Resistance Exercise	[A] Whole body PRT using weight machines [B] 2 x Week [C] 10 -15 RM (RPE 15) [D] 3 sets x 8 reps [E] 12 Weeks	**Anthropometry (Skinfolds)** Fat (%)	Exercise: ⇑ 4% Control: ⇑ 2%	Small (0.4)

Casteneda (2001) *Ann Intern Med*	RCT	• Control • Resistance Exercise	[A] Whole body PRT using weight machines [B] 3 x Week [C] 80% 1RM [D] 3 sets x 8 reps [E] 12 Weeks	**CT** Thigh Muscle CSA (cm^2)	Exercise: ⇑2 % Control: ⇓2 %	Small (0.2)

RCT, Randomised Controlled Trial; DXA, Dual X-Ray Absoptiometry; CT, Computerised Tomography; MRI, Magnetic Resonance Imaging; CSA, Cross Sectional Area; *, statistical significance declared (p<0.05); A, mode of exercise; B, frequency of exercise; C, intensity of exercise; D, training volume per session of exercise; E, length of intervention.

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Table 5.2. Baseline characteristics of all groups

Characteristic	Haemodialysis patients		Healthy participants	
	PRET	**SHAM**	**PRET**	**SHAM**
Age (years)	48 (18)	58 (15)	50 (15)	40 (17)
Sex (male/female)	7/2	6/4	2/2	0/4
Body mass index (kg/m^2)	25 (3)	26 (5)	30 (7)	25 (5)
Comorbid conditions				
Hypertension	5	4	1	1
Diabetes	0	2	0	0
Myocardial infarction	0	3	1	0
Number on medications				
Beta blockers	5	2	1	0
Ace inhibitors	3	4	0	0
Angiotensin	0	0	0	0
receptor blockers	2	5	0	0
Calcium channel blockers	1	2	0	0
Alpha blockers	0	4	0	1
Benzodiazepines	6	7	0	0
Erythropoiesis Stimulating Agents				
Etiology of HD				
Glomerulonephritis	4	5		
Infective/Obstructive	1	1	N/A	N/A
Hereditary	1	0		
Uncertain	3	4		
Dialysis Vintage (months)	46 (54)	66 (47)		
Kt/V_{urea}	1.34 (0.13)	1.50 (0.24)		
Hemoglobin (g·dL^{-1})	11.7 (1.8)	12.1 (2.1)	N/A	N/A
Albumin	41 (3)	42 (3)		
Serum bicarbonate (mmol·L^{-1})	22.4 (3.2)	22.5 (2.7)		
Serum potassium (mmol·L^{-1})	4.8 (1.0)	5.0 (0.6)		

PRET, progressive resistance exercise training; SHAM, attention control.

Table 5.3. Muscle volume, strength and physical functioning absolute data before and after the 12 week intervention period.

Outcome measure	Hemodialysis patients		Healthy participants		Analysis of change scores[a]	HD PRET vs. healthy PRET[b]	HD PRET vs. HD SHAM[b]	Healthy PRET vs. healthy SHAM[b]
	PRET	SHAM	PRET	SHAM	Statistical significance (*p* value)			
Muscle volume (cm^3)								
Pre	2822 (438)	2490 (601)	2877 (710)	2183 (527)	0.01	0.531	0.007	0.096
Post	2906 (489)	2380 (643)	3013 (863)	2151 (527)				
Knee extensor strength (N)								
Pre	179 (109)	151 (79)	382 (103)	239 (80)	0.002	0.636	0.012	0.064
Post	287 (86)	201 (77)	471 (191)	210 (31)				
Sit to stand (reps)								
Pre	11 (2)	10 (4)	21 (6)	23 (6)	0.003	0.005	0.270	0.004
Post	13 (3)	11 (5)	28 (8)	25 (7)				
8 foot get up & go (s)								
Pre	5.8 (1.2)	6.7 (1.8)	4.4 (0.2)	4.3 (0.7)	0.260	N/A	N/A	N/A
Post	5.0 (0.8)	6.2 (1.8)	3.8 (0.4)	4.5 (0.2)				
6 minute walk distance (m)								
Pre	532 (95)	460 (162)	536 (47)	559 (26)	0.026	0.701	0.446	0.012
Post	571 (101)	520 (160)	600 (54)	511 (38)				

PRET, progressive resistance exercise training; SHAM, attention control. [a], omnibus single factor analysis of variance; [b], *post hoc* independent *t*-test; N/A, not applicable (analysis of variance omnibus did not reach significance negating need for follow up test.

CHAPTER 6

General Discussion

Summary of Findings

The aim of this thesis was to investigate the effect of exercise on outcomes related to QoL and survival in CKD Stages four and five. In general, randomised controlled data suggested that exercise had some beneficial effect on outcomes relating to hospitalisation, morbidity and mortality in this patient population. The observed benefits of exercising outweighed its risks, thus supporting the initiative for adjunctive exercise prescription in the management of this disease state.

In the renal transplant population existing literature reveals that exercise has a beneficial effect on intermediate outcomes such as aerobic capacity and muscle strength, which possibly contribute to the improved QoL observed in this cohort. Exercise is recommended in this patient group with prescriptions based on guidelines provided for the specific co-morbidies of each individual patient. Home based interventions should be supported and encouraged by healthcare providers. In order to enable more detailed evaluation of exercise intervention on outcome measures in this cohort future studies require better quality interventions with strong research designs. The effects of exercise on endpoint outcome measures such as morbidity, hospitalisation and mortality still warrant investigation.

Despite current guidelines to implement post operative hand grip exercise for AVF maturation, a feasibility study revealed post operative forearm exercise to have little to no effect on AVF vasculature diameters, operative success or maturation. However, a similar exercise prescription implemented prior to AVF creation could potentially enhance surgery success.

Implementing intradialytic exercise proved effective at enhancing dialysis adequacy in terms of phosphate clearance and could potentially be prescribed for phosphate control. However, intradialytic exercise did not enhance dialysis adequacy

defined by small and middle molecule toxin clearance. Nevertheless exercise did not result in increased production of these uremic solutes. Therefore, haemodialysis patients that partake in exercise are not at risk of an increase in uremic toxin and harmful metabolite production as a result of exercising intradialytically.

High intensity progressive resistance exercise training during dialysis prevented muscle wasting, significantly increasing muscle volume and strength following three months of training. Preliminary evidence was provided to suggest that the anabolic response in the haemodialysis population was similar to that observed in healthy sedentary individuals, dispelling previous conceptions suggesting anabolic resistance in this cohort. Interestingly, despite changes in muscle volume and strength, these increases did not render the expected benefits in physical function.

Methodological Advancements

The strength of the studies reported in this thesis lies in their attempts to reduce risks of bias. The review of exercise in the transplant population was completed systematically and extensively evaluated the risk of bias. The objective and explicit methods employed in a systematic review limit bias and improve the reliability and accuracy of conclusions in comparison to a standard review. This review extensively assessed the risk of bias associated with each study and also addressed the 'FITT' (Frequency, Intensity, Type, Time) principle (Segura-Orti & Johansen, 2010) as a part of the quality assessment of intervention studies. These factors allow the appropriate interpretation of the available evidence. In addition, they encourage superior methodological designs in future studies. A further strength of the systematic review is that it reveals the exaggerated effect observed with weaker methodologies. For example, with regards to glucose tolerance, observational and cross sectional studies suggest higher habitual physical activity levels and exercise participation in glucose tolerant patients whereas interventional studies reveal disparate findings with small effect sizes on blood glucose concentrations.

Intervention studies in this thesis were of a randomized controlled nature, utilising gold standard outcome measures and implementing of superior exercise prescriptions that adhered to the 'FITT' principle. Based on exercise physiology these interventions could plausibly be effective at enhancing the respective outcome measures.

Albeit being a feasibility study, the investigation into forearm exercise for AVF maturation is the only known randomised controlled trial to investigate the effects of this type of exercise immediately post AVF surgery, despite clinical recommendations made in its favour (National Kidney Foundation, 1997). Furthermore, in comparison to previous research in the field (Kumar *et al.*, 2010; Oder, Teodorescu & Uribarri, 2003;

Rus *et al.,* 2005; Rodriguez Moran *et al.,* 1984), it encompassed a rigorous exercise prescription providing adequate progression and a sufficient exercise frequency and duration to theoretically have a physiological effect on the relevant outcome measures.

This feasibility study employed the use of duplex ultrasound as a non invasive technique to assess AVF vasculature parameters as outcome measures. The use of duplex ultrasound to assess anatomical and flow parameters of an AVF has been shown to have a high diagnostic value (Tordoir *et al.,* 1989) and is recommended by current clinical guidelines supported with a high evidence level (National Kidney Foundation, 1997). However, it should be noted that this technique is prone to suffer from operator dependency (Tordoir *et al.,* 1989) as was observed when assessing flow volume in this feasibility study. Future research should therefore ensure a single experienced vascular sonographer at each centre. Furthermore, new outcome measures to predict AVF maturation have recently come to light including venous compliance (King *et al.,* 2012) and pulse pressure measurements (Mengnjo *et al.,* 2012). These could possibly be considered as additional outcome measures in future trials.

With regards to intradialytic exercise prescription for dialysis adequacy, five other randomised controls have previously been reported in this area (Kong *et al.,* 1999; Parsons, Toffelmire & King-Van Vlack, 2004; Leung, 2004; Vaithilingam *et al.,* 2004; Adorati, 2000). The current study considered the prescription parameters of these previous studies in an attempt to implement a more effective exercise prescription. For example, in terms of exercise duration, Kong *et al.,* (1999) who showed a significant increase in Kt/V_{urea} as a result of exercise, implemented exercise for 60 minutes during dialysis with ten minute rest periods between exercise bouts. Alternatively, studies that revealed no increases in Kt/V_{urea} exercised for shorter durations (less than 30 minutes) and with longer rest periods (up to 60 minutes) (Parsons, Toffelmire & King-VanVlack, 2004; Leung, 2004; Parsons, Toffelmire & King-VanVlack, 2006; Adorati

2000). This observation inferred that if high blood flow to low perfusion tissues was not sustained for longer than 30 minutes it would not allow sufficient time to enhance small molecule clearance from these lean tissue areas. In this regard, using simulative equations Smye, Lindley & Will (1998) estimated that blood flow to low perfusion areas gradually increases during exercise over 20 - 30 minutes before reaching a plateau. In addition, in the current study exercise was prescribed at the end of dialysis which differs from previously reported studies that implement exercise during the first two hours of dialysis (Parsons, Toffelmire & King-VanVlack, 2004; Leung, 2004; Parsons, Toffelmire & King-VanVlack, 2006; Adorati 2000). As previously mentioned, the rationale for this was based on mathematical predictions stating that sustaining high blood flow to normally low flow tissue areas in the last 30 minutes of a 150 min dialysis session will almost completely eliminate post dialysis urea rebound (Smye, Lindley & Will 1998).

Further methodological strengths of this study lie in the closely controlled treatment parameters throughout the study. Trend files downloaded from the dialysis machines recorded treatment parameters at 2 s epochs throughout each dialysis session allowing extensive analysis and control over these confounding variables. Measurements of toxins in the serum as well as the gold standard measurement of toxins cleared in the waste dialysate by continuous sampling of spent dialysis (CSSD) provided a double pool insight into the kinetics of the measured solutes. However, a limitation lies within the high intraindividual variation of the CSSD measure reported in this study. Future research should take this into consideration and potentially adapt the CSSD equipment in attempt to enhance the reliability of this measure.

The investigation into progressive resistance training reported in this thesis adds to the randomised controlled data previously reported in four studies observing the effects of intradialytic resistance exercise on whole body composition measures

(Cheema *et al.,* 2007a; Cheema *et al.,* 2007b; Johansen *et al.,* 2006; Chen *et al.,* 2010). The current study adds methodological advancements to those previously reported (Cheema *et al.,* 2007a; Cheema *et al.,* 2007b; Johansen *et al.,* 2006) in that the novel equipment utilised allowed the prescription of a very high intensity of exercise as well as an adequate progression with gains in strength, both of which are deemed necessary to elicit an anabolic response (Kraemer *et al.,* 2002).

The current study also incorporated the gold standard body composition of magnetic resonance imaging providing a more accurate measure of muscle mass compared to other anthropometric and nutritional measures which tend to underestimate protein wasting (Mathur *et al.,* 2008). Furthermore, the measurement of muscle volume by magnetic resonance imaging provides a recommended endpoint of nutritional status in this patient population (Senior & Maroni,1999) in comparison to previous methods employed such as total body potassium or muscle fibre cross sectional area (Castaneda *et al.,* 2001). In fact, the use of differing body composition methods across trials in this area may provide a partial explanation in the disparity in the findings. For example, Casteneda *et al.,* (2001) reported a significant increase in total body potassium and muscle fibre cross sectional area following an outpatient resistance exercise programme yet no significant change in thigh muscle cross sectional area measured by computerized tomography was observed. In addition, Johansen *et al.* (2006) observed a significant increase in quadriceps cross sectional area as measured by magnetic resonance imaging, yet no significant change in lean body mass as measured by dual x-ray absorptiometry following an intradialytic resistance exercise programme.

A potential measure for future research could be to investigate changes in muscle quality by analyzing contractile tissue and intramuscular fat. This could be accomplished firstly by refining the scanning protocol implemented herein to obtain clearer images. These images can then be assessed for contractile tissue and

intramuscular fat by plotting signal intensity threshold histograms as shown in **Figure 6.1** (Holmback *et al.,* 2002).

Theoretical Physiology

The body's response to the stress of exercise can often provide interesting insights into physiological mechanisms in both healthy and diseased populations. It is beyond the scope of the studies reported in this thesis to directly explore the intricate molecular or genetic mechanisms underlying exercise responses in the CKD population. However, the results of the studies can inform physiological hypotheses regarding the mechanistic responses to exercise and also potential physiological abnormalities within this disease state.

Shear Stress and Arterial Remodelling. Sustained increases in blood flow lead to structural arterial remodelling. In response to acute increases in shear stress (the tangential force exerted by blood flow on the vessel wall) nitric oxide is released from the endothelial cells inducing a rise in intracellular smooth muscle cell cGMP resulting in vessel wall dilation (Dammers *et al.,* 2005b). When this haemodynamic milieu is chronic, structural remodelling such as an increase in vessel wall thickness is observed (Dammers *et al.,* 2005b). In this thesis, forearm exercise which induced acute hyperaemia, unexpectedly had no effect on proximal AVF vasculature cross sectional area. At first possible explanations for this discouraging finding were thought to be that either i) the forearm exercise prescribed did not allow sufficient and sustained increases in blood flow to allow structural remodelling or ii) the impaired endothelium dependent vasodilation observed in uremia (Morris *et al.,* 2000) due to a reduced stimulation of nitrogen oxide (Passauer *et al.,* 2005) could pose as resistance to the beneficial vascular effects of exercise.

However, despite this suspected endothelial dysfunction, normal vascular responses in the brachial artery have previously been observed in response to shear stress increases in CKD patients (Dammers *et al.,* 2005b). Additionally, increases in

forearm vasculature diameter have previously been reported in CKD patients participating in hand grip exercises on the non fistula arm or prior to AVF creation (Rus *et al.,* 2005) .

A similar ~5 fold increase in shear stress is observed in the radial artery acutely in response to the hyperaemia of hand grip exercise and chronically that of AVF creation (Girerd *et al.,* 1996; Gonzales *et al.,* 2009). It therefore appears surprising that additional vascular remodeling is not observed when theoretically speaking sheer stress should be acutely doubled by combining exercise with AVF formation. However, a possible explanation could lie in a finding reported by Dammers *et al.* (2005b) who inferred that the large increase in blood blow associated with AVF formation exceeds the adaptation capacity of the radial arteries. Therefore, it could be hypothesised that further increasing shear stress through exercise would be futile as the challenge imposed to the arterial system by the AVF formation already exceeds the vascular adaptation capacity.

Kinetic Modeling of Uremic Toxins. Although exercise successfully increased phosphate clearance, the discouraging findings in relation to small and middle molecule clearance following exercise encouraged an exploration into the dialytic kinetics of the measured toxins. The aim of this discussion was not to prove the accuracy of one kinetic model over another but to explain these findings. Kinetic models are largely derived from simulations and, as biological and epidemiological data in their support is lacking (Eloot, Schneditz & Vanholder, 2012), it should be noted that these models are debatable.

With regards to the small molecule urea, the hypothesis that intradialytic exercise would increase urea clearance was based on a parallel regional blood flow kinetic model. This model separates organ systems to a high or low flow systems according to their specific blood perfusion (Schneditz, Platzer & Daugirdas, 2009) (**Figure 6.2.**). The

model assumes that delayed urea removal is related to low perfusion of the muscle tissue compartment and that increased blood flow to low perfusion tissue will result in a greater urea clearance (Schneditz *et al.,* 1995; Schneditz & Daugirdas, 2001). Simulated mathematical equations based on this model have suggested that increasing blood flow to low perfusion tissue by exercise hyperemia towards the end of dialysis would significantly increase urea clearance and almost completely eliminate urea rebound (Smye, Lindley & Will, 1998). However, the biological findings reported in this thesis do not support this model as hyperemia to the low perfusion muscle tissue did not have an effect on neither urea clearance nor urea rebound. Alternatively, these finding could be explained by the classic serial diffusion model which consists of simple connections between intra and extracellular compartments (Eloot, Schneditz & Vanholder, 2012) (**Figure 6.3**). This model incorporates a total body distribution of urea (Eloot, Schneditz & Vanholder, 2012) whereby the rapid transfer of urea from the intracellular to the extracellular compartment results in a precipitous equilibration of whole body urea (Metry *et al.,* 1993). Within this model, intracorporeal changes in blood flow would not affect urea kinetics and therefore this classic model could provide support for the finding that increased dialysis time enhanced urea clearance whilst intradialytic exercise did not.

The biological finding that $beta_2$-microglobulin clearance tended to be increased with a longer dialysis duration over intradialytic exercise is consistent with classical serial modeling which is based on intercompartmental transfer. In the case of $beta_2$-microglobulin, its high transfer coefficient resulting in slow intercompartmental transfers appears to be the rate limiting factor of its removal (Leypoldt, 2005). Thus increasing intracorporeal blood flow would have no effect on the membrane transfer coefficient of this molecule whilst longer dialysis would allow more time for the transfer of this molecule across relevant membranes. Again, the notion that our findings

are consistent with serial kinetic modeling as opposed to the parallel model are supported by a recent beta$_2$-microglobulin modeling investigation carried out by Maheshwari *et al.* (2011). The authors of this study established a regional blood flow model for beta$_2$-microglobulin based on the assumption that hyperemia would result in an increased capillary surface area as well as an increased membrane pore size ultimately leading to enhanced toxin removal and thus reduced rebound. However, when the effect of exercise was simulated using this model there was no effect on the toxin rebound ratio. The authors state that both cardiac output and blood flow to differing perfusion regions are less important model parameters whilst toxin distribution volume and inter-compartmental clearance coefficients are more important parameters.

Phosphate differs greatly from the previously mentioned uremic toxins as it presents with a four pool kinetic model during dialysis. A biphasic regulation of phosphate occurs whereby phosphate in released from a third and fourth pool when phosphate levels reach low and critically low levels respectively during the later stages of dialysis (Spalding, Chamney & Farrington, 2002). The physiologic mechanisms behind the increased phosphate removal during intradialytic exercise are unknown. However, it could be hypothesised that when exercising during the latter half of dialysis the phosphate produced from the muscle as a result of energy metabolism (Sorlie *et al.,* 1982) acts as a potential fifth pool prohibiting the need for phosphate release from the third and fourth pools. When exercise is complete, the excess serum phosphate released from the muscle is utilized for energy replenishment leading to reduced serum phosphate levels (**Figure 6.4**).

Anabolic Resistance. Previous discouraging findings in response to intradialytic resistance exercise for skeletal muscle anabolism (Cheema *et al.,* 2007a; Cheema *et al.,* 2007b; Johansen *et al.,* 2006) have led to an underlying theory that CKD patients may in fact be resistant to the anabolic effects of exercise due to an irregularity in the insulin-

like growth factor 1 (IGF-1)/growth hormone (GH) axis (Mak, Cheung & Roberts, 2008; Burd, Wall & van Loon, 2012). In healthy individuals resistance exercise stimulates skeletal muscle hypertrophy via mechanical and hormonal responses which activate signaling pathways promoting protein synthesis and reducing protein degradation. With regards to the hormonal response, resistance exercise results in an increase in GH which, when fitted into membrane receptors initialises several downstream signals leading to protein synthesis. In addition GH leads to increased IGF-1, a hormone which stimulates proliferation and differentiation of stem cells. However, in CKD there appears to be an IGF-1 insensitivity in that IGF-1 binding proteins, usually cleared through the kidney, are increased thereby decreasing the bioavailability of IGF-1 (Mak, 2008). Furthermore, a diminished IGF-1 gene expression in response to supramaximal increases in GH have been reported in CKD rat models (Mak, 2008). However, this theory had has not yet been fully tested in this patient population. Thus research warranted an exercise intervention deemed most appropriate for increases in skeletal muscle mass as was implemented in this thesis. The current findings revealed that skeletal muscle mass increased in CKD patients following high intensity progressive resistance exercise. Furthermore, although interpreted with caution due to a smaller sample size, this anabolic response appeared to be similar to that observed in healthy individuals thus questioning the previous conceptions regarding anabolic resistance. Therefore despite the hormonal irregularities reported in the disease state (Mak *et al.,* 2011) they do not deter from the mechanisms behind skeletal muscle anabolism.

Mechanisms of Increased Physical Function. Of great interest was the lack of a physical function response to the reported progressive resistance training in CKD patients despite significant increases in muscle volume and strength. As small increases in physical function were observed in the control group a possible explanation could be

that there was a potential learning effect for the functional tests; variability in this learning effect may have masked any potential increases in these measures (Hopkins, 2000). However, this does not explain neither the significant increase in physical function observed in the healthy group participating in the exact same intervention nor the consistently repeated finding showing no increase in objective functional measures following intradialytic resistance training in this population (Cheema *et al.,* 2007b; Johansen *et al.,* 2006; Chen *et al.,* 2010).

A further possible explanation may be that exercising in the dialysis environment could imply restrictions to the range of motion of exercises therefore limiting their functional benefit. However, this does not explain the increases in strength observed with intradialytic training (Cheema *et al.,* 2007b; Johansen *et al.,* 2006; Chen *et al.,* 2010) and furthermore, the increases in physical function observed in the healthy participants carrying out exercises with the same range of motions as the haemodialysis patients.

The fact that increases in physical function have been observed following similar interventions in other disease states (Lemmey *et al.,* 2009) implies that the explanation lies within factors corresponding to chronic kidney disease. However, this explanation is eliminated when increases in physical function are consistently reported following aerobic exercise intervention in this patient cohort (Heiwe & Jacobson, 2011).

This finding could give us an insight into the mechanisms behind increased physical function in dialysis patients. Usually, in healthy individuals, changes in physical function with increased muscle mass are partly due to an increased number of motor neurons (McArdle, Katch & Katch, 2001). However 60 – 100% of dialysis patients present with peripheral neuropathies characterised by segmental demyelination and axonal degradation and furthermore motor neurons have been shown to be depolarised before dialysis due to hyperkalemia (Krishnan, Pussell & Kiernan, 2009).

As well as this, myopathies in the form of muscle fibre splitting and degradation, nuclear knots and fatty infiltration are also common in this patient population (Diesel *et al.*, 1993). These factors could potentially inhibit changes in physical function through motor unit changes. It could be speculated that the physiological stimuli of aerobic exercise that are responsible for changes in physical function, such as mitochondrial biogenisis (Lanza, Sreekumaran & Nair, 2010) for example, are the more dominant mechanisms behind changes in physical function following exercise in this population. However, this hypotheses is only speculative and the observed increase in strength leaves it very much up to debate. Irrespectively, the mechanisms behind physical function in haemodialysis patients make for an interesting area for future research.

Limitations

Although specific limitations are highlighted in each chapter, the major limitation to this thesis lies in the generalisation of extrapolating the results across the CKD population. Anecdotally speaking, in most exercise studies in haemodialysis patients those who volunteer to participate in the exercise interventions are usually the patients who present with a better self reported quality of life and superior physical health, fitness and function. Additionally, the strict exclusion criteria implemented for ethical purposes in these studies prohibit patients of a poorer health status from participating in exercise, when in fact these patients would possibly show greater beneficial responses to increased physical activity. As a result, the findings of the studies reported herein may possibly be underestimated due to the selection bias of the samples.

Conclusions and Future Directions

The systematic review of already existing findings in the kidney transplant population reported exercise to enhance outcomes such as aerobic capacity, strength and quality of life. This thesis reported evidence that exercise has a beneficial effect on dialytic solute clearance, skeletal muscle anabolism and strength as well as a potential for enhanced AVF success and maturation. The findings add to the myriad of health benefits of exercise reported in the CKD population including increased physical fitness and function (Heiwe & Jacobson, 2011), cardiovascular adaptations (Cheema 2008), quality of life (Heiwe & Jacobson, 2011) and longevity of life (O'Hare *et al.*, 2003). All harms reported in the studies were resolved without late effects or sequalae inferring that exercise in this cohort is safe and its benefits outweigh any potential risks.

Yet, despite the wealth of literature documenting the health benefits of exercise as well as clinical guidelines recommending exercise participation in dialysis patients (K/DOQI Workgroup 2005) and even furthermore, the fact that the majority of patients strongly agree that a sedentary lifestyle poses a health risk (Delgado & Johansen, 2012), exercise is still not prescribed as part of routine care in the CKD population. For example, in comparison to cardiovascular disease whereby ~400 cardiac rehabilitation programmes are run in the UK (Lewin *et al.*, 2010), only 10% of the 72 nephrology centres in the UK offer some form of exercise intervention as adjunctive therapy to CKD patients (British Renal Society Renal Rehabilitation Network, 2012). Reported barriers to exercise appear to be factors such as fatigue, lack of motivation and shortness of breath (Delgado & Johansen, 2012). Of more importance appears to be the barrier of deficient counseling of physical activity amongst healthcare providers with staff reporting a lack of confidence in their ability to administer information regarding exercise (Delgado & Johansen, 2010). In addition, there appears to be a disparity in

physician and patient opinions whereby a large proportion of physicians assume dialysis patients to be uninterested in physical activity when in fact patient surveys suggest that this is the case in only ~4% of patients (Delgado & Johansen, 2012). This problem needs to be addressed as patients trust the advice of their health care providers (Schutzer & Graves, 2004) and therefore staff can play a pivotal role in the initiation and maintenance of exercise behaviour.

As addressed in all chapters of this thesis, exercise prescriptions should follow the FITT principle which should be based on the basic exercise physiology of the desired outcome in order to enhance efficacy and efficiency of the intervention.

Although the positive findings relating to exercise participation reported in this thesis provide noteworthy and interesting information, the requisite for more large scale, multicentred, randomised controlled trials investigating hard outcome measures such as quality of life and mortality in CKD patients is still outstanding. Furthermore, the essential establishment of clear guidelines regarding the most effective exercise prescriptions are warranted in order to implement exercise as an adjunctive therapy in CKD on a large scale.

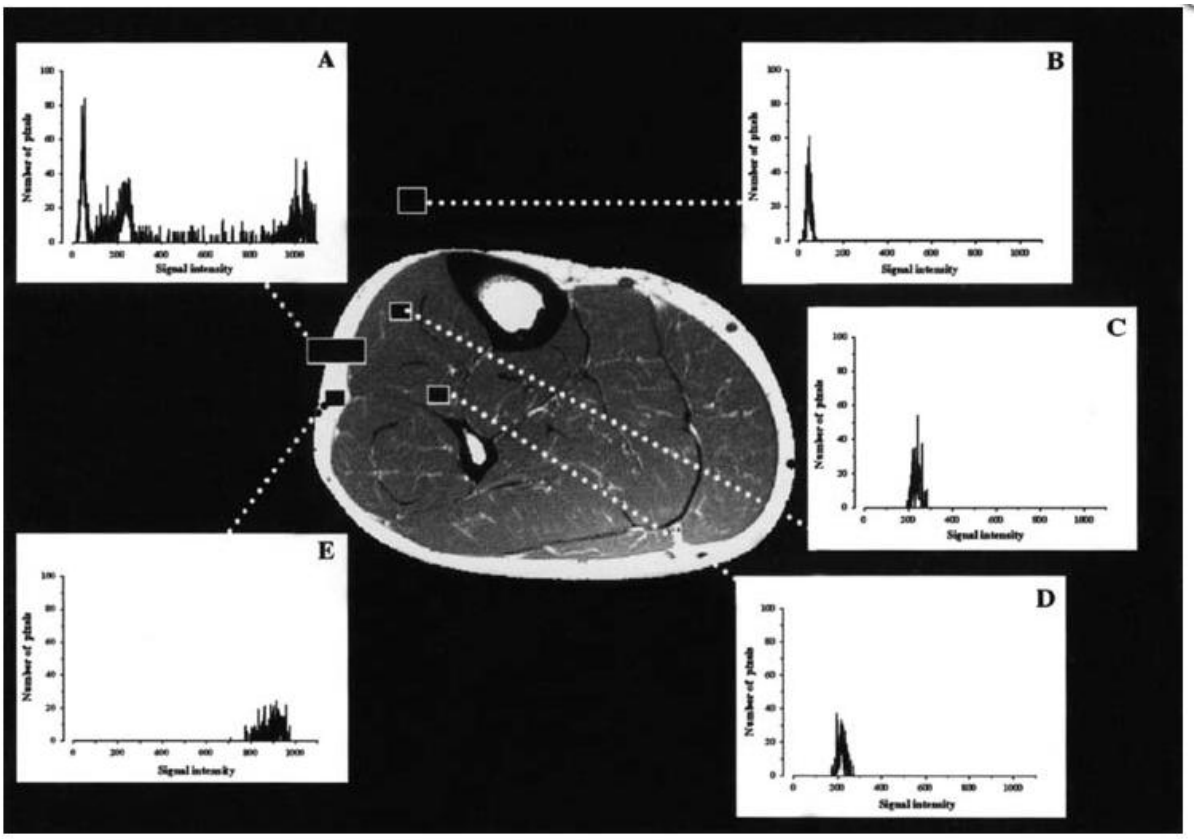

Figure 6.1. An illustration taken from (Holmback *et al.*, 2002) of the method used to determine contractile and non contractile components of muscle from a cross sectional magnetic resonance image slice of the ankle dorsiflexor muscles. Signal intensity thresholds are determined for five clear different regions of interest (ROI). A: a mixture of contractile and non contractile tissue; B: background image; C & D: two smaples of what appears to be contractile tissue; E: subcutaneous fat only. From the signal intensity plots it can be seen that contractile tissue lies between 100 and 300 and intramuscular fat lies between 780 and 990. The ROI (e.g. a certain muscle group) is then selected and the percentage of pixels that lie between 100 and 300 will represent the percentage of contractile tissue and likewise for intramuscular fat. This method of analysis has been shown to be highly reliable (Holmback *et al.*, 2002) .

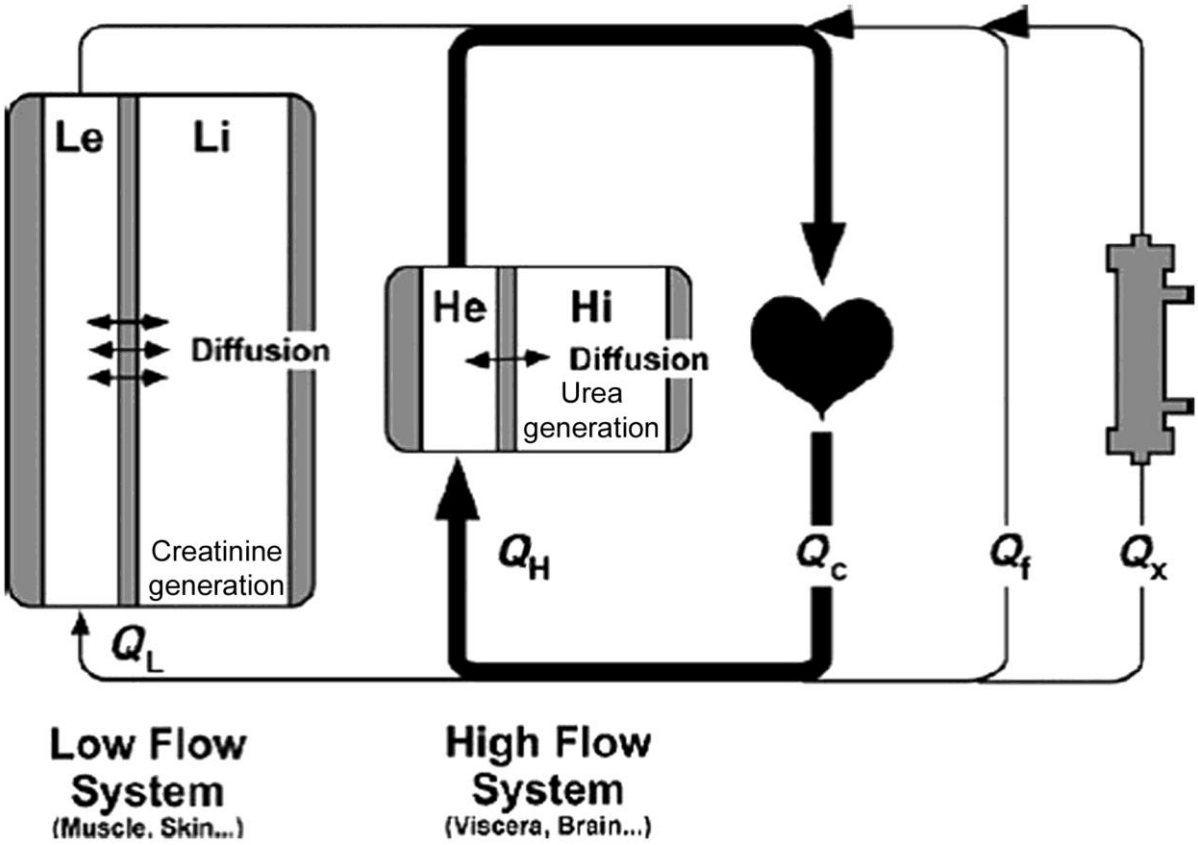

Figure 6.2. The parallel regional blood flow kinetic model (Schneditz, Platzer & Daugirdas 2009). He, extracellular high-flow system; Hi, intracellular high-flow system; Le, extracellular low-flow system; Li, intracellular low-flow system; Q_L, low flow; Q_H, high flow; Q_c, cardiac output; Q_f, fistula flow; Q_x, extracorporeal blood flow.

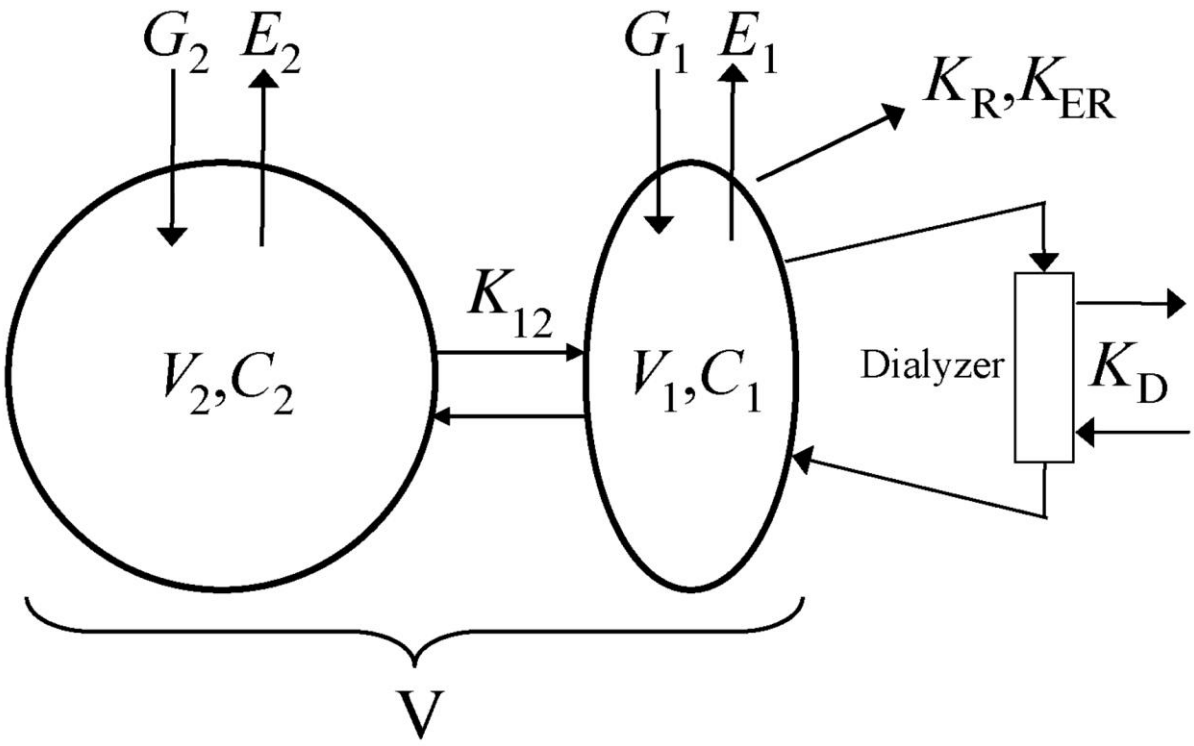

Figure 6.3. The classic two compartmental serial model (Eloot, Schneditz & Vanholder 2147). V_1, plasma volume; V_2, non-plasmatic volume; V, total distribution volume; C_1, plasma concentration; C_2, non-plasmatic concentration; G_1 and G_2, generation rate in V_1 and V_2; E_1 and E_2, metabolic elimination in V_1 and V_2; K_R, renal clearance; K_{ER}, extra renal clearance; K_D, dialyser clearance; K_{12}, intercompartment clearance.

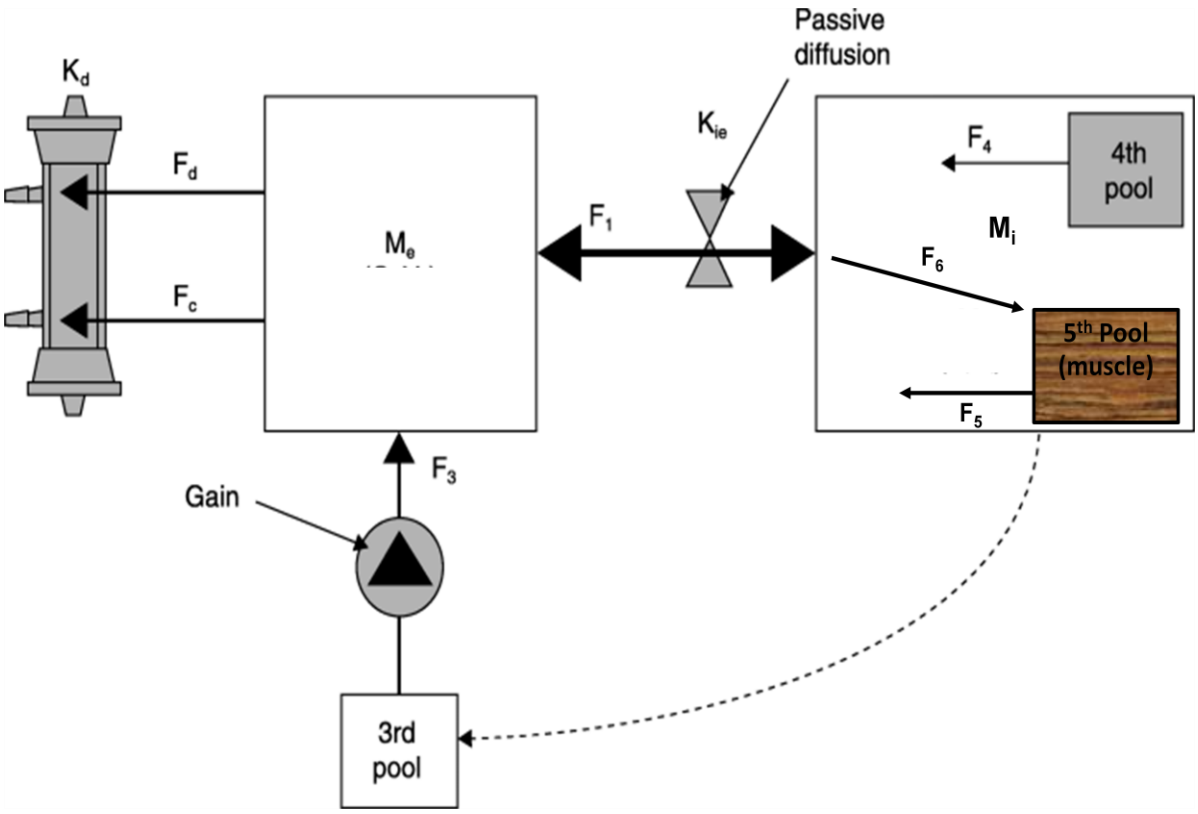

Figure 6.4. A schematic representation of the four-compartment model adapted from Spalding, Chamney & Farrington (2002) describing the kinetics of phosphate during both short and long haemodialysis treatments as well as intradialytic exercise during the end of dialysis . This model is a conventional two-compartment model describing diffusive (F_d) and convective (F_c) fluxes across the dialysis membrane comprising a dialyzer phosphate clearance (K_d). Also indicated here is intercompartment phosphate flux (F_1) governed by the intercompartmental mass transfer coefficient (K_{ie}). The unique aspect of this model is the addition of a third pool or compartment that releases phosphate into the extracellular compartment (F_3) based on the difference between the calculated intracellular and intrinsic intracellular target intracellular phosphate concentration and a fourth pool or compartment that releases phosphate intracellularly to protect the intracellular environment from dangerously low phosphate concentrations (F_4) (Leypoldt, 2005). During intradialytic exercise it is hypothesised that the muscle acts as a fifth pool releasing phosphate (F_5) and preventing the regulatory requirement of phosphate release from the third and fourth pools. Following exercise serum phosphate is utilized to replenish energy stores (F_6). The intracellular and extracellular compartments are indicated by subscripts i and e, respectively.

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