THE EFFECT OF EXERCISE ON SOLUTE REMOVAL DURING HAEMODIALYSIS IN END-STAGE RENAL DISEASE

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AUTHORS DECLARATION

This study represents original work by the author. It has not been submitted in any other form to any other Tertiary Institution. Where use of the work of others was made, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Renal Units at the Newcastle and Bloemfontein Medi-Clinic Hospitals, South Africa owned by E W Pope and Associates with the academic advice of Prof J K Adam from Durban University of Technology, Department of Biomedical and Clinical Technology.

Signed: _____

Mrs S Singh

I hereby certify that the above statement is correct.

Signed: _____

Prof J K Adam (PhD)

DEDICATION

To my parents Ramesh and Geetha Singh, who have given their unconditional love, understanding and support throughout my life.

To my husband Sudir Sahadeo, who has encouraged and inspired me during this special venture.

Most importantly, To Almighty God, who has made everything possible through his divine blessings.

ABSTRACT

Introduction

Exercise assessment, counseling and training are not widely offered to patients with chronic kidney disease. Haemodialysis patient's participation in exercise and an adequate assessment of exercise effects on haemodialysis outcome are needed so that more interventions can be developed to improve the well being of those patients with chronic kidney disease. Exercise is not routinely advocated in patients with end-stage renal disease receiving maintenance haemodialysis. Lack of widespread awareness of exercise in haemodialysis literature may be contributing to these shortcomings in clinical practice.

Purpose of the study

This study was aimed to establish the effect of exercise during haemodialysis on pedal oedema and solute removal. This is the first time that such a study was undertaken in dialysis units in South Africa.

Methodology

In a quasi-experimental design, thirty-four end-stage renal failure patients on three times weekly haemodialysis program from Bloemfontein and Newcastle MediClinic Renal Units participated in the study. Ethical approval for the study was obtained from Durban University of Technology Ethics Committee. Seventeen patients were in the intervention group (aged between 25 and 60) and seventeen in the control group (aged between 18 and 60). The intervention group did not exercise for the first three months of the study in order to establish a baseline period. Thereafter, exercising took place from the fourth to the ninth month. Patients pedaled on an exercise cushion for fifteen minutes every hour to achieve a total of sixty minutes of exercise over a four-hour dialysis session. Patients in the control group did not pedal on the exercise cushion during the nine-month study period. Pre and post haemodialysis measurements of creatinine, urea and potassium using the Alkaline Picrate, Urease and Ion Selective Electrode methods respectively were done for each patient monthly over the nine month period. Oedema of the lower limb was evaluated by measuring the right and left ankle

circumference, in centimetres before and after dialysis. Urea Kt/V was also measured before and after haemodialysis for each patient over the study period.

Results

Statistical analysis of results showed a significant 30% reduction in urea levels and a 46% reduction in creatinine levels in the intervention group at the end of the nine month period, a 12% reduction in the potassium levels in the intervention group which was 4% more than the control group. The urea Kt/V in the intervention group showed a 9% greater reduction than the control group. There was a significant improvement in oedema of 45% of the right ankle for the first three months of exercise and thereafter there was an increase in ankle size in the last three months which was a 13% reduction in oedema compared to baseline. There was a significant improvement in oedema of 60% of the left ankle for the first five months of exercise and thereafter there was an increase in ankle size in the last month which showed a 25% reduction compared to baseline. The reason for the increase in ankle size in both ankles in the last three months is inconclusive and future investigation is recommended.

Conclusion

The results of this study demonstrated benefits of exercise during haemodialysis on solute removal and oedema perhaps due to the acute increases in blood flow and therefore increasing perfusion of skeletal muscles.

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LIST OF ABBREVIATIONS

ADH	- antidiuretic hormone
ATP	- adenosine triphosphate
AVP	- arginine vasopressin
BUN	- blood urea nitrogen
CAPD	- continuous ambulatory peritoneal dialysis
CKD	- chronic kidney disease
CrCl	- creatinine clearance
CRP	- C reactive protein
DOQI	- dialysis outcomes quality initiative
ESRD	- end stage renal disease
GFR	- glomerular filtration rate
GLD	- glutamate dehydrogenase
HD	- haemodialysis
INT	- intervention group
KT/V	- dialysis efficiency formula
mmol/L	- millimoles per litre
µmol/L	- micromoles per litre
NADH	- nicotinamide adenosine dehydrogenase
NKF	- national kidney foundation
PCR	- polymerase chain reaction
SD	- standard deviation
SUN	- serum urea nitrogen

V_2 receptors- vasopressin receptors

CHAPTER ONE

INTRODUCTION

Patients with chronic kidney disease are known to be inactive and have reduced physical functioning and performance. These patients remain inactive because of several reasons. Some of these include reduced effort tolerance and muscle strength caused by anaemia, cardiovascular and pulmonary disease, altered skeletal muscle metabolism, myopathic changes associated with chronic renal failure per se, malnutrition and physical deconditioning (Kutner, Brogan and Fielding 1991). Exercise assessment, counseling and training are not widely offered to patients with chronic kidney disease. Haemodialysis patient's participation in exercise and an adequate assessment exercise effects on haemodialysis outcome are needed so that more interventions can be developed to improve the well being of those patients with chronic kidney disease. All patients on haemodialysis (HD) should be encouraged to participate in moderate physical activity, especially those who are weak and the elderly. Exercise should be initiated at a moderate intensity in patients with chronic kidney disease and progress slowly as tolerated in order to avoid injury and discontinuation of exercise.

The positive influence of regular exercise on health, quality of life, and physical exercise capacity, endurance, and muscle strength, social, professional and emotional status should be encouraged in patients with chronic kidney disease. Exercise is not routinely advocated in patients with end-stage renal disease receiving maintenance haemodialysis. Lack of widespread awareness of exercise in haemodialysis literature may be contributing to these shortcomings in clinical practice.

Haemodialysis is a life-saving renal replacement treatment for patients with end-stage renal disease. However, prolonged survival is associated with various functional and morphological disorders from almost all systems (Valderrabano, Berthoux, Jones and Mehls, 1996). These lead to severe functional limitations, which add to the cost of medical care and remain an important poor prognostic factor in predicting future morbidity and survival (Marcelli, Stannard, Conte, Held, Locatelli and Port, 1996).

Most dialysis patients have diminished work capacity, including increased difficulties with activities of daily living and lower levels of employment (Kutner, Brogan and Fielding 1991). The presence of comorbidities that exist in patients with end-stage renal disease on haemodialysis include diabetes mellitus, anaemia, coronary artery disease, hypertension and peripheral vascular disease (Locatelli and Manzoni, 1999). As a consequence, many patients still experience significant clinical and psychological problems and their quality of life is poor (Mingardi, Cornalba, Cortinovis, Ruggiata, Mosconi and Apolone, 1999).

This study aimed to establish the effect of exercise during haemodialysis on pedal oedema and solute removal. Similar experiments have been conducted with success internationally where the standards in medical services are expected to be higher than a third world country (Parsons, Toffelmire and King-VanVlack, 2004). This is the first time that such a study was undertaken in dialysis units in South Africa. The results of this study will help us establish whether it is possible to implement routine exercise for patients with renal failure during haemodialysis in order to improve solute levels and oedema.

CHAPTER TWO
STUDY BACKGROUND AND LITERATURE REVIEW

2.1 STUDY BACKGROUND

2.1.1 The Kidney

The human body consists of 60 – 70% fluid - an isotonic salt solution containing a variety of dissolved chemicals and cellular material. The distribution of body water between the intracellular, interstitial and intravascular compartments is tightly controlled along electrical and physiochemical lines. This control of fluid and electrolyte balance is essential to prevent the human from either drying out or drowning. The principle organ involved in this balance is the kidney (Neligan, 2008).

The human kidneys are two bean-shaped organs, one on each side of the backbone. They Represent about 0.5% of the total weight of the body, but receive 20–25% of the total arterial blood pumped by the heart. Each contains from one to two million nephrons (Figure 2.1). (http://users.rcn.com/jkimball.me.ultranet/BiologyPages/k/kidney.html#nephron).

There are three major anatomical demarcations in the kidney: the cortex, the medulla, and the renal pelvis. The cortex receives most of the blood flow, and is mostly concerned with reabsorbing filtered material. The medulla is a highly metabolically active area, which serves to concentrate the urine. The pelvis collects urine for excretion.

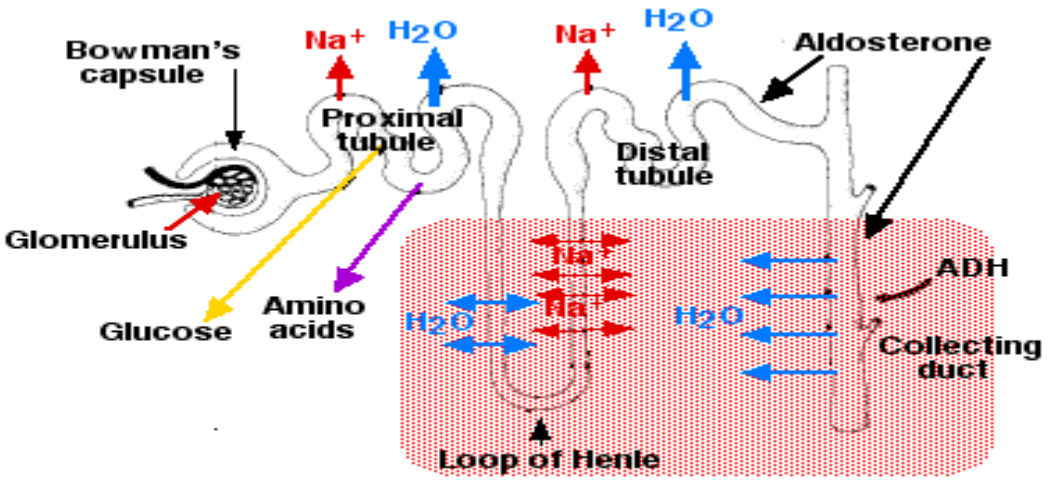

Figure 1: The Nephron

(http://user.rcn.com./jkimball.me.ultranet/BiologyPages/k/kidney.html#nephron).

2.1.2 Functions of the Kidney

The two main functions of the kidney are as follows:

1. It regulates fluid and electrolyte balance by filtration, secretion and reabsorption.
2. It is an endocrine organ – it activates both erythropoeitin (for production of red blood cells) and vitamin-D (which regulates calcium metabolism). It also produces renin (in the afferent arteriole) which affects various aspects of water and electrolyte homeostasis (NIH Publication, 2009).

The functional unit of the kidney is the nephron (Figure 2.1). There are five parts of the nephron:

1. The glomerulus, which is the blood kidney interface, plasma is filtered from capillaries into the Bowman's capsule.
2. The proximal convoluted tubule, which reabsorbs most of the filtered load, including nutrients and electrolytes.

3. The loop of Henle, which, depending on it's length, concentrates urine by increasing the osmolality of surrounding tissue and filtrate.
4. The distal convoluted tubule, which reabsorbs water and sodium depending on needs,
5. The collecting system, which collects urine for excretion. There are two types of nephrons, those localized to the cortex, and those extending into the medulla. The latter are characterized by long loops of Henle, and are more metabolically active (Neligan, 2008).

Renal blood flow is 25% of cardiac output (1200 ml/minute). Of this, renal plasma flow is about 660ml/minute, and 120ml/minute is filtered out of the blood and into the nephron. Ultimately approximately 1.2ml of this fluid is excreted as urine (1% of filtered load). The major determinants of GFR are:

1. Renal blood flow and renal perfusion pressure.
2. The hydrostatic pressure difference between the tubule and the capillaries.
3. The surface area available for ultrafiltration. The rate at which fluid is filtered by the glomerulus is the glomerular filtration rate (GFR) (NIH Publication, 2009).

2.1.2.1 Proximal Tubule

In the proximal tubule, 2/3 of filtered sodium, water and chloride are reabsorbed along with most of the filtered glucose, amino acids, bicarbonate and vitamins. The mechanism of reabsorption is for sodium to be actively pumped out of the tubule, and water to follow passively (Nelgan, 2008).

2.1.2.2 Loop of Henle

There are two parts to the loop, a thin descending limb and a thick ascending limb. The purpose of this anatomical structure is to allow both concentration and dilution of the urine, by way of the influence of hormones on distal structures. A

sodium-potassium-chloride (1Na+:1K+:2Cl-) pump actively extracts these electrolytes from the tubular fluid in the thick ascending limb. The latter is impermeable to water, but the descending limb is permeable. Sodium and chloride are actively pumped out of the fluid, such that the fluid arriving at the distal tubule is hypotonic (dilute), the presence of these electrolytes in the interstitial tissue increases tissue osmolality, and water flows along the osmotic gradient from the descending limb into the interstitium . The fluid left in the tubule becomes hyperosmolar (in relation to normal plasma) (Nelgan, 2008).

2.1.2.3 Distal Tubule and Collecting Ducts

The result of this “countercurrent multiplier” system is threefold:

1. The high concentration of sodium and chloride (and urea) in the medullary interstitium makes this part of the kidney hyperosmolar.
2. Fluid delivered to the distal convoluted tubule is hypotonic. So, as this fluid passes down through this tubule and the collecting duct, it is exposed to very high osmolar pressures in the surrounding tissues. If the patient is dehydrated, the pituitary gland produces ADH (antidiuretic hormone/vasopressin), which makes the collecting ducts permeable to water, and water is rapidly reabsorbed along the concentration gradient. If not, dilute urine is excreted.
3. Extracellular fluid volume depends on the amount of sodium in the body, so it is essential that the kidney is capable of conserving sodium. If the extracellular volume drops, a complex series of neurohormonal interactions lead to the release of aldosterone, which makes the collecting ducts permeable to sodium, which is absorbed (Nelgan, 2008).

2.1.2.4 Formation of Urine

The nephron makes urine by filtering the blood of its small molecules and ions and then, reclaiming the needed amounts of useful materials. Surplus or waste

molecules and ions are left to flow out as urine. In 24 hours the kidneys reclaim ~1,300 g of NaCl , ~400 g $NaHCO_3$,~180 g glucose and almost all of the 180 liters of water that entered the tubules.

The steps are as follows:

- Blood enters the glomerulus under pressure.

This causes water, small molecules (but not macromolecules like proteins) and ions to filter through the capillary walls into the Bowman's capsule. This fluid is called nephric filtrate. As table 1 shows, it is simply blood plasma minus almost all of the plasma proteins. Essentially it is no different from interstitial fluid (http://users.rcn.com/jkimball.me.ultranet/BiologyPages/k/kidney.html#nephron).

Table 1: Composition of plasma, nephric filtrate and urine (each in g/100 ml of fluid)
(http://users.rcn.com/jkimball.me.ultranet/BiologyPages/k/kidney.html#urine.

Component	Plasma	Nephric Filtrate	Urine	Concentration	% Reclaimed
Urea	0.03	0.03	1.8	60X	50%
Uric acid	0.004	0.004	0.05	12X	91%
Glucose	0.10	0.10	None	-	100%
Amino acids	0.05	0.05	None	-	100%
Total inorganic salts	0.9	0.9	<0.9–3.6	<1–4X	99.5%
Proteins and other macromolecules	8.0	None	None	-	-

- Nephric filtrate collects within the Bowman's capsule and then flows into the proximal tubule.

- Here all of the glucose, and amino acids, >90% of the uric acid, and ~60% of inorganic salts are reabsorbed by active transport.
    - The active transport of Na^+ out of the proximal tubule is controlled by angiotensin II.
    - The active transport of phosphate (PO_4^{3-}) is regulated (suppressed by) the parathyroid hormone.
- As these solutes are removed from the nephric filtrate, a large volume of the water follows them by osmosis (80–85% of the 180 liters deposited in the Bowman's capsules in 24 hours).
- As the fluid flows into the descending segment of the loop of Henle, water continues to leave by osmosis because the interstitial fluid is very hypertonic. This is caused by the active transport of Na^+ out of the tubular fluid as it moves up the ascending segment of the loop of Henle.

In the distal tubules, more sodium is reclaimed by active transport, and still more water follows by osmosis. Final adjustment of the sodium and water content of the body occurs in the collecting ducts. (http://users.rcn.com/jkimball.me.ultranet/BiologyPages/k/kidney.html#nephron).

2.1.3 Urea, Creatinine, Potassium, Urea KT/V and Oedema

2.1.3.1 Blood Urea Nitrogen (BUN)

Blood urea nitrogen known, as urea is a product formed after the metabolism of amino acid in the liver and is eliminated by the kidneys as a waste product. The blood urea nitrogen (BUN) test is a measure of the amount of nitrogen in the blood in the form of urea, and a measurement of renal function. Urea is a substance secreted by the liver, and removed from the blood by the kidneys (Guyton and Hall, 2005). The liver produces urea in the urea cycle as a waste product of the digestion of protein. Normal human adult blood should contain between 7 to 21 mg of urea nitrogen per 100 ml (7-21 mg/dl) of blood. Individual

laboratories may have different reference ranges, and this is because the procedure may vary (Rao, Grimm, Le and Bhushan, 2008).

The most common cause of an elevated BUN, azotemia, is poor kidney function, although a serum creatinine level is a somewhat more specific measure of renal function. A greatly elevated BUN (>60 mg/dl) generally indicates a moderate-to-severe degree of renal failure. Impaired renal excretion of urea may be due to temporary conditions such as dehydration or shock, or may be due to either acute or chronic disease of the kidneys themselves (Rao et al., 2007).

An elevated BUN in the setting of a relatively normal creatinine may reflect a physiological response to a relative decrease of blood flow to the kidney (as seen in heart failure or dehydration) without indicating any true injury to the kidney. However, an isolated elevation of BUN may also reflect excessive formation of urea without any compromise to the kidneys (Rao et al., 2007).

Increased production of urea is seen in cases of moderate or heavy bleeding in the upper gastrointestinal tract (e.g. from ulcers). The nitrogenous compounds from the blood are reabsorbed as they pass through the rest of the gastrointestinal tract and then broken down to urea by the liver. Enhanced metabolism of proteins will also increase urea production, as may be seen with high protein diets, steroid use, burns, or fevers.

A low BUN usually has little significance, but its causes include liver problems, malnutrition (insufficient dietary protein), or excessive alcohol consumption. Over hydration from intravenous fluids can result in a low BUN. Normal changes in renal blood flow during pregnancy will also lower BUN (Rao et.al. 2007). Urea itself is not toxic. However, BUN is a marker for other nitrogenous waste. Thus, when renal failure leads to a buildup of urea and other nitrogenous wastes (uremia), an individual may suffer neurological disturbances such as altered cognitive function (encephalopathy), impaired taste (dysgeusia) or loss of appetite (anorexia). The individual may also suffer from nausea and vomiting, or

bleeding from dysfunctional platelets. Prolonged periods of severe uraemia may result in the skin taking on a grey discolouration or even forming frank urea crystals ("uremic frost") on the skin.

Because multiple variables can interfere with the interpretation of a BUN value, GFR and creatinine clearance are more accurate markers of kidney function. Age, sex, and weight will alter the "normal" range for each individual, including race. In renal failure or chronic kidney disease (CKD), BUN will only be elevated outside "normal" when more than 60% of kidney cells are no longer functioning. Hence, more accurate measures of renal function are generally preferred to assess the clearance for purposes of medication dosing (Rao et al., 2007).

2.1.3.2 Creatinine

Creatinine (from the Greek *kreas*, flesh) is a break-down product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). Chemically, creatinine is a spontaneously formed cyclic derivative of creatine. Creatinine is a metabolic product formed from muscle creatine and is eliminated by the kidneys as a waste product. Due to the inability of the kidneys to excrete creatinine in patients with renal failure, the blood creatinine levels are raised above normal blood creatinine levels and have to be reduced by dialysis (Table 2.1) (Guyton and Hall, 2005).

Creatinine is chiefly filtered out of the blood by the kidneys, though a small amount is actively secreted by the kidneys into the urine. There is little-to-no tubular reabsorption of creatinine. If the filtering of the kidney is deficient, blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which reflects the GFR. The GFR is clinically important because it is a measurement of renal function. However, in cases of severe renal dysfunction, the creatinine clearance rate will be "overestimated" because the active secretion of creatinine will account for a larger fraction of the total creatinine cleared. Ketoacids, cimetidine and

trimethoprim reduce creatinine tubular secretion and therefore increase the accuracy of the GFR estimate, particularly in severe renal dysfunction (In the absence of secretion, creatinine behaves like inulin) (Delanghe, De Slypere, De Buyzere , Robbrecht , Wieme and Vermeulen 1989).

A more complete estimation of renal function can be made when interpreting the blood (plasma) concentration of creatinine along with that of urea. BUN-to-creatinine ratio (the ratio of urea to creatinine) can indicate other problems besides those intrinsic to the kidney; for example, a urea level raised out of proportion to the creatinine may indicate a pre-renal problem such as dehydration. Men tend to have higher levels of creatinine because they have more skeletal muscle than women. Vegetarians have been shown to have lower creatinine levels (Delanghe et al., 1989).

2.1.3.3 Potassium

Potassium is an electrolyte useful in certain quantities for the normal functioning of the body. Excess amounts of potassium are toxic and harmful to the body and are excreted by the kidneys to maintain healthy normal levels. When a patient is in renal failure, the kidneys are impaired and are unable to remove excess potassium putting the patient's life at risk. The patient would have to receive dialysis to bring down the potassium levels (Table 2.1) (Guyton and Hall, 2005).

2.1.3.4 Urea Kt/*V*

The Urea Kt/V is a number used to quantify haemodialysis and peritoneal dialysis treatment adequacy; where,

K = dialyzer clearance of urea

t = dialysis time

V = patient's total body water

In the context of hemodialysis, Kt/V is a dimensionless number. In peritoneal dialysis, it is dimensionless only by definition.

It was developed by Frank Gotch and John Sargent as a way for measuring the dose of dialysis when they analyzed the data from the National Cooperative Dialysis Study (Gotch and Sargent, 1985). In hemodialysis the US National Kidney Foundation Kt/V target is 1.3, so that one can be sure that the delivered dose is at least 1.2. In peritoneal dialysis the target is 2.0/week (National Kidney Foundation, 2000).

Measurement of dialysis efficiency in patients: The Kt/V formula

This formula is commonly used in haemodialysis units to determine the efficiency of dialysis (Daugirdas, Blake and Ing, 2006). This enables the staff to establish whether patients are provided with good quality treatment. According to the National Kidney Foundation (NKF), Dialysis Outcomes Quality Initiative (DOQI) guidelines, the minimum prescribed dose of dialysis should be a Kt/V of 1.2. Patient survival has been shown to increase in association with increases in Kt/V up to 1.2 (National Kidney Foundation, 1997).

The Kt/V for urea (Kt/V urea) is as follows:

$$Kt/V = -\ln(R - 0.03) + (4 - 3.5 \times R) \times UF/W$$

R = *post/pre plasma urea nitrogen ratio*

UF = *ultrafiltrate volume (litres) removed*

W = *post dialysis weight (kg)*

2.1.4 Sodium and Water

2.1.4.1 Sodium

Although 97% of the sodium has already been removed, it is the last 3% that determines the final balance of sodium - and hence water content and blood pressure - in the body. The reabsorption of sodium in the distal tubule and the collecting ducts is closely regulated, chiefly by the action of the hormone aldosterone.
(http://users.rcn.com/jkimball.me.ultranet/BiologyPages/k/kidney.html#urine

2.1.4.2 Water

- The hypertonic interstitial fluid surrounding the collecting ducts provides a high osmotic pressure for the removal of water.
- Transmembrane channels made of proteins called aquaporins are inserted in the plasma membrane greatly increasing its permeability to water. (When open, an aquaporin channel allows 3 billion molecules of water to pass through each second).
- Insertion of aquaporin-2 channels requires signaling by vasopressin (also known as arginine vasopressin [AVP] or the antidiuretic hormone [ADH]).
    - Vasopressin binds to receptors (called V2 receptors) on the basolateral surface of the cells of the collecting ducts.
    - Binding of the hormone triggers a rising level of cAMP within the cell.
    - This "second messenger" initiates a chain of events culminating in the insertion of aquaporin-2 channels in the apical surface of the cell.

The release of vasopressin (from the posterior lobe of the pituitary gland) is regulated by the osmotic pressure of the blood.

- Anything that dehydrates the body, such as perspiring heavily,
    - increases the osmotic pressure of the blood;
    - turns on the vasopressin → V2 receptors → aquaporin-2 pathway.

  The result:

    - As little as 0.5 liter/day of urine may remain of the original 180 liters/day of nephric filtrate.
    - The concentration of salts in the urine can be as much as four times that of the blood. (But not high enough to enable humans to benefit from drinking sea water, which is saltier still.)
- If the blood should become too dilute (as would occur after drinking a large amount of water),
    - Vasopressin secretion is inhibited.
    - The aquaporin-2 channels are taken back into the cell by endocytosis.

The result: a large volume of watery urine is formed (with a salt concentration as little as one-fourth of that of the blood) (http://users.rcn.com/jkimball.me.ultranet/BiologyPages/k/kidney.html#urine).

2.1.5 Kidney Failure

Chronic renal failure may be defined as a glomerular filtration rate (GFR) below 30 ml per minute (Walls, 1995). Symptoms and complications of uraemia often occur when GFR is less than 15 ml per minute. Chronic renal failure affects every aspect of life of the patients who suffer it (Warnock, 1996).

Kidney failure occurs when the kidney is unable to function normally with less than 10% of its function. Some of the main causes of kidney failure are as follows (Warnock, 1996):

- Diabetes which damages the nephrons in the kidneys

- Hypertention or untreated high blood pressure which damages the nephrons causing nephrosclerosis
- Inflammation which causes swelling of the nephrons resulting in Glomerulonephritis and Collagen disease such as Lupus, an auto-immune disease.
- Obstructions in the urinary system such as kidney stones or structural birth defects.
- Chronic Infection of the kidney and urinary tract may lead to kidney failure such as cystitis and pyelonephritis.
- Hereditary conditions such as polycystic disease and glomerulonepritis.
- Other causes of kidney failure include accidents, injury caused by medication, drugs, poisons and radiation.

When the kidney is unable to function normally, there is a build-up of fluids in the body resulting in oedema and swelling and a build-up of waste products such as urea, creatinine and uric acid. These elevated waste products result in uremia. The symptoms of uremia are: headache, drowsiness or confusion, nausea and vomiting, itching, tiredness, diarrhea, decrease or increase in frequency of urination, swelling (oedema), shortness of breath, hypertension, puffiness of the face and eyes, decreased sexual interest, loss of appetite, loss of concentration and thirst. Solutes levels (sodium, potassium and hydrogens) are raised when the kidneys are not functioning because of the inability to reabsorb and secrete. Hormones such as rennin, angiotensin II, prostaglandins and bradykinin that participate in systemic and renal haemodynamics are not secreted as well as calcium, phosphorus and bone metabolism (1,25-dihydroxyvitamin D3 or calcitriol). Erythropoietin is not produced by the kidney which results in anaemia (Warnock, 1996).

2.1.5.1 Oedema

Oedema is an excessive increase in body fluid in the extravascular, intercellular compartment which causes swelling and discomfort in the body. Fluid overload not responding to diuretic administration is a common problem associated with chronic renal failure resulting in oedema (Guyton and Hall, 2005). Fluid overload is a common problem in the patients with renal insufficiency and multisystem disease (Prazella and Khan, 2006; Daugirdas, Blake and Ing, 2006).

This fluid overload leads to oedema i.e. fluid accumulation in the lungs, brain cells, limbs, face and around the body. Patients on chronic haemodialysis usually gain fluid between two dialysis sessions, which sometimes in excess causes oedema of the ankles and legs as seen in Figure 2. Patients are advised to restrict fluid intake to reduce the onset of oedema. This is often very difficult for most patients to control and they cannot eradicate this problem of oedema completely. Inactivity and lack of exercise does not improve this condition but rather aggravates the oedema causing an increase in the swelling of the limbs (Prazella and Khan, 2006).

Figure 2: Pedal Oedema in a Patient with Renal Failure (photographed at the research unit).

Volume control is a key component of treatment of haemodialysis patients. The role of pedal oedema as a marker of volume is unknown. It has been shown that pedal oedema correlates with cardiovascular risk factors such as age, body mass index, and left ventricular mass but does not reflect volume in haemodialysis patients (Agarwal, Andersen and Howard, 2008).

2.1.6 Problems encountered by Dialysis Patients

2.1.6.1 Psychological

The most common problem encountered in dialysis patients is depression (including suicide), uncooperative behaviour, sexual dysfunction, and difficulties pertaining to occupation and rehabilitation (Levy 1993; Ahmad, Khan, Mustafa and Khan, 2002).

2.1.6.2 Nutritional

Malnutrition is common in dialysis patients due to a poor intake of food. Usually the primary cause is anorexia. However, economic, cultural, and psychosocial factors may play a major role in some patients. Other patients with poor food intake may be responding obediently to numerous dietary prohibitions without being able to find sufficient alternative foods that they like and that are available to them (Blumenkrantz, 1980; Himmelfarb, 2005).

2.1.6.3 Haematological Abnormalities

Anaemia in dialysis patients occurs when the kidney loses its ability to produce erythropoietin as it loses other functions. Anaemia begins to develop when the glomerular filtration rate falls below 20-30 ml/minute/1.73m^2. (Daugirdas, Blake and Ing, 2006; Ahmed et. al, 2002; Himmelfarb, 2005).

2.1.6.4 Bone Disease

Bone disease in dialysis patients is due primarily to the effect of secondary hyperparathyroidism. The cause of hyperparathyroidism is hypocalcemia and diminished circulating calcitriol levels due to reduced 1-hydroxylation of 25-hydroxyvitamin D3 in the kidney (Kaye, 1990; Himmelfarb, 2005).

2.1.6.5 Skin Disorders relating to the Uremic Syndrome

The skin is a frequently affected organ in uremia. Skin disorders in the dialysis patient related to uremia are pruritis, xerosis, hyperkeratosis penetrans, uremic pigmentation, purpura, uremic frost, bullous dermatosis, calciphylaxis and nail changes. Drug related skin disorders are hypertrichosis, acne and drug hypersensitivity. Skin disorder related to primary renal disease is cutaneous vasculitis (Daugirdas, Blake and Todd, 2006).

2.1.6.6 Eye Disease

Kidney disorders do not directly affect vision or change the morphology of the eyes. In advanced renal failure, conjunctival erythema termed red eyes of uraemia may be noted when high plasma phosphorus levels induce corneal and conjunctival precipitation of calcium pyrophosphate. Ophthalmic complications of diabetes mellitus are the most prevalent eye disorders noted in dialysis patients (Friedman, 1986).

2.1.6.7 Lungs and Pleura

Lung oedema, pleural effusion and infection are the dominant pulmonary complications in dialysis patients. Other problems encountered include dyspnea during haemodialysis and peritoneal dialysis, respiratory failure secondary to

hyperkalemia, hypophosphatemia or carbohydrate loading and sleep apnea. (Kaupke and Vaziri, 1991).

2.1.6.8 Heart and Circulation

The prevalence of cardiovascular disease in the dialysis population is elevated, primarily because of an increased presence of the usual risk indicators for atherosclerosis, especially hypertension and diabetes. Factors specifically associated with uremia such as hypertriglyceridemia, hyperparathyroidism, vascular calcification, abnormal calcium and phosphorus metabolism and elevated serum levels of urate and oxalate may also play a role. (Daugirdas, Blake and Ing ,2006; Ahmed et al, 2002; Himmelfarb, 2005).

2.1.6.9 Rheumatologic Disease

Rheumatologic conditions encountered most frequently in dialysis patients are carpal tunnel syndrome and various forms of arthropathy. Muscle weakness may be an important clinical problem in some patients and spontaneous tendon rupture may also occur (Daugirdas, Blake and Ing, 2006).

2.2 LITERATURE REVIEW

2.2.1. INTRODUCTION

For over twenty years attempts have been made to improve the physical performance of patients suffering from chronic kidney disease by physical exercise (Goldberg, Geltman and Hagberg, 1983; Jette, Pasen and Cardarelli, 1977; Painter and Zimmerman, 1983; Zabetakis, Gleim, Pasternack, Saranti, Nikolas and Michelis, 1982). Studies have proved that regular exercise enhances physical ability of patients with chronic kidney failure and other chronic conditions and lessens the severity of accompanying diseases such as arterial hypertension, renal anaemia, hyperlipidemia, as well as depression that renal patients experience (Carney, Templeton and Hong, 1987; Clyne, Ekholm, Jogestrand, Lins and Pehrsson, 1991; Goldberg, Geliman and Gavin, 1986; Hagberg, Goldberg, Ehsani, Heath, Delmez and Harter, 1983; Harber, Scheidegger, Gritnig and Frey 1985; Painter, Carison, Carey, Paul and Myll, 2000).

Patients with chronic renal failure on haemodialysis are at increased risk of cardiovascular disease. This is due, mainly to a higher prevalence of established atherosclerotic risk factors, including diabetes mellitus, hypertension, dyslipidemia, and physical inactivity as well as unique chronic renal failure risk factors. Accordingly, cardio-respiratory insufficiency, left ventricular dysfunction and atherosclerosis may often antedate, and hence contribute to exercise intolerance and to increased morbidity and mortality (Himmelfarb, 2005).

In haemodialysis patients the application of exercise training programs is effective in improving cardiorespiratory capacity, as demonstrated mainly by increasing VO2 peak. More-over, better left ventricular systolic function at rest, as well as at effort following training was suggested (Deligiannis, Kouidi, Tassoulas, Gigis Tourkantonis and Coats, 1999). The increase of cardiac vagal

outflow and the decrease of sympathetic over- activity at rest are significant beneficial results of exercise training in haemodialysis patients (Deligiannis et al., 1999; Daul, Volker, Alberty, Holmann and Philipp, 1997).

Daul and colleagues (1997), concluded that exercise training during dialysis is the first kind of renal exercise rehabilitation which is accepted by a relevant number of patients. This is carried out over months and even years. It has been found to have positive effects on the physical and psychosocial situations of the patients, which are similar to those of outpatient group exercises. Some patients who trained exclusively during dialysis, decided to participate in group exercise in a gymnasium as well. One 32-year-old patient was able to improve his physical capacity to such an extent, that he was able to successfully run a half-marathon. Prior to the exercise program this patient had suffered from obvious reactive depression (Daul et al., 1997). To patients suffering from chronic kidney disease exercise and movement offer a variety of benefits that should be made use of to a higher extend in the future. Even with respect to the financial aspects, few resources are needed to establish an exercise program and to reduce the total treatment cost of haemodialysis patients significantly by exercise rehabilitation (Daul et al., 1997).

As early as the 1980's attempts were made to utilize the time of haemodialysis treatments for physical training (Krause, Abel, Bennhold and Koepchen, 1989; Painter, Nelson and Hill 1986). Painter and colleagues (1986), conducted ergometric training sessions with haemodialysis patients using a conventional cycle ergometer positioned in front of the dialysis chair. They demonstrated that this kind of exercise training improved endurance capacity, and in some hypertensive patients even decreased blood pressure. Despite these positive effects, this type of exercise program was not realized on a broad scale during the following years.

In the mid 1990's, a more complex and varied exercise program was developed which included not only bed-cycle training, but also gymnastics to improve strength, co-ordination, and flexibility (Daul and Krause, 1997). In addition, bed ergometers were used which could easily be fixed to the dialysis chair or dialysis bed, and could be used in a sitting or in a half-lying position. Some of these bed-cycles had an electric motor and therefore these devices were not only suitable for active exercise but for passive movement during haemodialysis (Konstantinidou, Kaukouvou, Kouidi, Deligiannis and Tourkantonis, 2002). Although exercise during haemodialysis proved to have positive effects on haemodialysis patients in the mid 1990's, these positive effects were not intensively studied, especially the effects of exercise during haemodialysis on blood solute levels and oedema.

2.2.2 Airogym – Exercise Device

Scurr and Perry (2001), consultant vascular surgeons at Middlesex and University College Hospitals, conducted a research on long haul passengers before and after flying to establish a link between flying and blood clotting. Their work had included looking at methods of preventing blood clots during flying and the medical evaluation of the Airogym. The Airogym was designed specifically to address two common problems associated with long haul flying, i.e., ankle swelling and blood clotting. Although usually regarded as having a bleeding tendency, patients with end-stage renal disease on haemodialysis are at risk of venous thrombosis, which usually occurs soon after a subclavian vein catheter, arterio-venous fistula or arterio-venous graft is inserted or as a late event. Early thrombosis is usually due to technical factors and requires surgical correction. Late thrombosis is most commonly preceded by poor blood flow through the fistula but may be precipitated by a period of dehydration, hypotension or hypercoagulability. Swelling and oedema occurs due to fluid overload when patients do not respond to diuretic administration (Scurr and Perry, 2001). They often feel fatigued and are unable to join an exercise program at the gymnasium

or do any strenuous activities. This inactivity further increases the risk of developing deep vein thrombosis, swelling and oedema due to poor blood circulation. Both can be attributed to stagnation of the circulation. Anybody sitting or standing for long periods of time will notice ankle swelling and pain in the lower legs. Fortunately, in the majority of passengers the clots dissolved without causing any apparent symptoms or signs, and leaving no long-term damage. On occasions the blood clot can grow and a segment can break off and travel to the lungs. There are two problems associated with blood clots. Firstly, the presence of a clot in the lung, and secondly, an effect which may take many years to manifest itself, namely the development of the post thrombotic limb (Scurr and Perry, 2001).

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The Airogym was designed specifically to promote the flow of blood through the deep veins. By pressing down the footpad, veins in the foot are compressed, squeezing blood into the main veins in the calf. The pressure involved in squeezing the foot causes muscular contractions of the calf muscles promoting the flow of blood through the main veins. Results show an improvement in peak velocity blood flow up to five times. The device prevented venous stasis and reduced the risk of developing blood clots and also prevented ankle swelling (Scurr and Perry, 2001).

2.2.3 Effects of Exercise on Solute Removal during Haemodialysis

Exercise during haemodialysis is beneficial and may have positive effects on patients with end-stage renal disease (Sun, Chen, Jia and Wang, 2002). Tests were carried out by Kong, Tattersal Greenwood and Farington, 1999), who conducted research on eleven patients (aged 32-78 years) on haemodialysis (4-58 months). Patients pedalled on a cycle for 15 minutes at sub maximal workload followed by a rest to achieve a total of 60 minutes exercise. Plasma concentrations of urea, creatinine and potassium were measured pre and post dialysis. The Kt/V (dialysis efficiency formula) was calculated and the results

were compared. The results of this research showed that the rebounds of all three solutes were reduced significantly following exercise. The rebound of urea decreased from 12.4% to 10.9%, creatinine from 21.2% to 17.2% and potassium from 62% to 44%. Kt/V reduction Ratios increased significantly as a result Kt/V urea from 1.00 to 1.15 and reduction ratio urea from 0.63 to 0.68. This study confirmed that exercise increased the efficiency of dialysis by reducing the solute rebound of solutes due to increased perfusion to skeletal muscles.

2.2.4 The Effects of Exercise on Nutrition and Hydration during Haemodialysis

Patients with end-stage renal disease undergoing haemodialysis and peritoneal dialysis are functionally limited as a consequence of their physical, emotional and social problems. Exercise intolerance is a major problem in chronic renal failure.
An investigation carried out by Zaluska, Bednarek-Skublewska and Ksiazek, 2002), demonstrated that nutrition and hydration status improved with exercise training during haemodialysis in patients with renal disease. They made use of stationary cycling. The aim of the study was to evaluate the effect of cycling exercise in ten haemodialysis patients during a six-month period (including each of the dialysis sessions) on nutrition, dialysis adequacy and fluid parameters as measured by biochemical and bioimpedance parameters. The results showed a significant increase in serum albumin concentration and Kt/V, and a decrease in serum CRP (C Reactive Protein) have been observed after six months of regular stationary cycling during haemodialysis. Relative changes (pre-post haemodialysis) in extracellular water compartment had significantly increased after six months of observation period. Stationary cycling training during haemodialysis is recommended as safe, effective and practical in end-stage renal disease patients (Zaluska et al., 2002).

2.2.5 Effects of Exercise on Dialysis Adequacy during Haemodialysis

Another investigation was conducted at Xuan Wu Hospital, China by Sun et al., (2002). The objective of this study was to investigate the effect of exercise during haemodialysis on adequacy of dialysis. Twenty patients on haemodialysis participated in this study. Twenty studies were performed and each study consisted of a pair of haemodialysis treatments. The blood and dialysate flow rates; dialyser and treatment times were the same. An adapted exercise cycle was attached to the dialysis bed. The patients in the exercise group pedaled on the exercise cycle throughout dialysis and had a 5-10 minute rest if they needed, while the patients of the control group had no exercise cycle. Blood urea nitrogen, serum creatinine and uric acid were measured just before dialysis, immediately after dialysis and 60 minutes after dialysis. Furthermore online dialysis monitor detected the Kt/V. The results of this investigation indicated that in the exercise group, after haemodialysis blood urea nitrogen, serum creatinine and uric acid were significantly lower than those in the control group. Kt/V was significantly higher in the exercise group than those in the control group, while nPCR showed no significant difference between the two groups. It was therefore concluded that exercise during haemodialysis is a practicable new way to improve dialysis efficacy.

2.2.6 Cardiac Adaptations following Exercise Training in Haemodialysis Patients

Cardiovascular disease is the leading cause of morbidity and mortality in end-stage renal disease patients (Parfrey and Harnett, 1994; Rostand, Brunzell, Cannon and Victor, 1991). A high proportion of patients on haemodialysis have a prevalence of conventional cardiovascular risk factors and also suffer from cardiac abnormalities, including hyperlipidemia, diabetes, coronary artery disease, congestive heart failure, arrhythmias and hypertension (Fleischman, Bower and Salahudeen, 2001; Ritz, 1996). In haemodialysis patients, the probability of having an acute myocardial infarction is 10% per year and of sudden cardiac death is 9% (Foley, Parfrey, Sarnak, 1998; Owen, Madore and

Brenner, 1996). The importance of cardiovascular complications has become even more apparent with increased prevalence of diabetes mellitus and the change of the demographics regarding their age and sedentary life-style. Mortality statistics demonstrate that the death rate is approximately 3,5 times that of the general population (Lowrie, Zhang and LePain, 1990; Owen et al., 1996). At least half of the deaths in these patients result from cardiovascular disease (Sarnak and Levey, 1998).

2.2.6.1 Effects of Exercise Training on Cardiorespiratory Capacity

Cardiorespiratory fitness level in haemodialysis patients is reported to be dramatically low and relative to patients with other severe chronic disease, like heart failure and chronic obstructive pulmonary disease (Sietsema, Hlatt, Esler, Adler, Amato and Brass, 2002). Their maximal aerobic capacity measured as peak VO2, is reported to be from 15-25ml/kg/min, values that are approximately 50% of the corresponding healthy sedentary age-matched individuals (Kettner-Melsheimer, Weiss and Huber, 1987; Kouidi, 2001; Painter and Moore, 1994). Increasing participation in exercise training programs and/or daily activities is a recommended way to improve work capacity and health outlook among end-stage renal disease patients (Kutner, Brogan and Fielding, 1991; Oberley, Sadler and Steolt, 2000).

The combination of treatment of anaemia and encouragement of physical activity are the most important interventions to minimize the physical functioning of patient on dialysis (Johanson, 1999). All the different approaches to exercise training in HD patients have beneficial effects on their work capacity. Increases in peak VO2 between 20-40% have been reported in most studies after exercise training lasting 3-12 months (Kouidi, 2001; Koufaki, Nash and Mercer, 2002; Painter, 1994). Haemodialysis patients can successfully adhere to long-term physical training programs with considerable improvements in cardiorespiratory fitness. A four year supervised exercise training group of dialysis patients led to a

70%, a 53% and a 52% increase in VO2 peak, exercise testing duration and ventilatory threshold correspondingly (Kouidi, Grekas, Deligiannis and Tourkantis, 2004).

2.2.6.2 Effects of Exercise Training on Cardiac Function

Cardiac hypertrophy that leads to congestive heart failure is a major contribution to the limited survival on haemodialysis patients (Parfrey and Harnett, 1994). This hypertrophy is usually followed by left ventricular dilation and causes systolic and diastolic dysfunction (Greaves, Gamble, Collins Whalley and Sharpe, 1994).

Chronic and intense exercise training in haemodialysis patients is reported to cause beneficial cardiac morphological and functional adaptations (Deligiannis et al., 1999). Long term exercise training in haemodialysis patients caused an increase of the ventricular end-diastolic volume and a decrease in end-systolic volume, as well as an increase in the interventricular septum and the left ventricular posterior wall thickness (Deligiannis et al., 1999). Similar adaptations to exercise training were also described on healthy sedentary subjects and cardiac patients (Maron, 1986; Rinder, Miller and Ehsani, 1999). Ejection fraction, stroke volume and cardiac output are found to be significantly increased both at rest and during submaximal exercise in haemodialysis patients following a six month supervised intense training program (Deligiannis et al., 1999). Exercise training seems to have beneficial effects in the management of hypertension in haemodialysis patients, mainly by reducing the peripheral vascular resistance (Hagberg et al., 1983).

Multifactorial cardiac rehabilitation, including exercise training and dietary intervention, with and without the use of lipid-altering drugs, effected regression or limited progression of angiographically, documented coronary atherosclerosis (Gielen, Schuler and Hambrecht, 2001). In dialysis patients it is supported that

six months supervised moderate intensity exercise training may enhance cardiac vagal tone at rest, as assessed noninvasively by 30% increase in the value of time-domain heart rate variability (Deligiannis et al., 1999).

In summary, there have been demonstrated definite long-term benefits of renal exercise rehabilitation programs, in terms of cardiorespiratory capacity and exercise tolerance.

2.2.7 Exercise Rehabilitation and Skeletal Muscle Benefits in Haemodialysis Patients

End-stage renal disease patients on haemodialysis are characterized by poor exercise tolerance and debilitation symptoms, despite advances in dialysis procedures and erythropoietin use. Specifically, the muscle strength and endurance are diminished as a result of skeletal muscle dysfunction and atrophy. It has been known for many years that muscular weakness and fatigue, myoclonus and cramps, in dialysis patients have traditionally been attributed as factors that limit physical activity (Gardenas and Kutner, 1982; Laville and Fouque, 1995). Anaemia, malnutrition, neurohormonal dysfunction which, in turn, alter the anabolic/catabolic balance, cardiac dysfunction, skeletal myopathy and inactivity are closely related to these abnormalities and, thus, to exercise intolerance (Diesel, Enims, Knight, Noakes, Swanepoel, Van Zyl Smith, Kaschula and Sinclair-Smith, 1993).

2.2.7.1 Muscle Morphology and Metabolism in Uremia

Biopsy studies in haemodialysis patients reveal that skeletal muscles commonly have abnormal structure and function, characterized as “ uremic myopathy”

(Diesel et al., 1993; Floyd, Ayyar, Barwick, Hudgson and Weightman, 1974). Several factors contribute to this myopathy, like malnutrition and reduce energy intake, impaired protein synthesis and amino acid metabolism, favouring catabolism over anabolism, prolonged inactivity, side-effects of excess parathyroid hormone and other uremic toxins, abnormalities in Vitamin D metabolism, hypophosphatemia and other electrolyte abnormalities and abnormal activation of the autonomic nervous system (Braubar, 1983; Thompson, Kemp, Tylor, Ledingham, Radda and Rajagopalan, 1993). Carnitine deficiency in haemodialysis patients due to poor interstinal absorption of dietary L-carnitine and also because the reabsorption by the kidneys are impaired, resulting in increased urinary loss of L-carnitine. In addition, many dialysis patients have signs of peripheral denervation, resulting mainly from chronic uremic environment (Diesel et al., 1993). Thus, muscular atrophy often appears secondary as a consequence of “uremic neuropathy” (Stein, Schmidt, Sperschneider, Keil, Michael, Hedwry, Funfstuck and Gassel, 1986). Reduced skeletal muscle blood flow in some dialysis patients may, therefore explain the changes in both oxidative enzyme activity and capillarity (Bradley, Anderson, Evans and Cowley, 1990).

2.2.7.2 Effects of Exercise Training in Uremic Myopathy

Exercise in haemodialysis patients have shown significant favorable changes on the number and structure of mitochondria, the size of oxidative fibres in the capillary fibres in muscles (Gollnick, Armstrong, Saubert, Plehl and Saltin, 1972; Hambrecht, Niebauer, Fiehn, Kalberer, Offner, Hauer, Riede, Schlierf, Kubler and Schuler, 1995).

Exercise training improves the ability of muscles to use oxygen and optimize the effect of increased haematocrit resulting from erythropoietin therapy (Painter and Moore, 1994). Moore and colleagues found an upward trend for succinate dehydrogenase activity and phosphofructokinase activity increased after twelve

weeks of aerobic training (Moore, Parsons, Stray- Gundersen, Painter, Brinker and Mitchell, 1993). After six months intense exercise training, including both aerobic and strengthening exercise on haemodialysis, exercise performance was increased, by improving muscle atrophy in haemodialysis patients (Kouidi, Albani, Natsis, Megalopoulos, Gigis, Guiba-Tziampiri, Deligiannis and Tourkantonis, 1998). Exercise was found to decrease muscle protein catabolism and enhance the sensitivity of muscle to insulin in uremic animals (Davis, Karl, Goldberg and Harter, 1983).

2.2.8 The Negative Effects of Exercise Insufficiency on Muscle Strength in Patients with Chronic Renal Failure

Patients with chronic renal failure complain of muscle weakness and loss of strength. Diagnosis can begin with a patient history distinguishing weakness from fatigue. The pattern and severity of weakness, associated symptoms, medication use, family history and insufficient exercise helps the doctor determine whether the cause of a patients weakness is electrolyte-induced, drug-induced, metabolic, genetic, rheumatologic, inflammatory, endocrine, neurologic or infectious. A comprehensive evaluation of these patients includes a thorough examination and coordination of appropriate laboratory, radiologic, electro-diagnostic and pathologic studies as well as measuring muscle strength directly (Muscular Dystrophy Association, 2006)

2.2.8.1 Definitions

Determining the cause of muscle weakness involves distinguished primary weakness from fatigue or astenia, a common condition that differs from, but often overlaps with muscle weakness. Fatigue describes the inability to continue performing a task after multiple repetitions; in contrast, a patient with primary weakness is unable to perform the first repetition of the task. Asthenia is a sense of weariness or exhaustion in the absence of muscle weakness. Muscle

weakness is common in people who have kidney disease, depression, chronic fatigue syndrome, sleep disorders, chronic heart and lung disease. (Muscular Dystrophy Association, 2006)

2.2.8.2 History of Muscle Weakness

Once muscle weakness has been diagnosed the doctor should ask the patient about disease onset and progression. Acute onset may indicate infection or stroke. Subacute onset may implicate drugs, electrolytes, or inflammatory or rheumatologic disease. Chronic progressive muscle weakness is the classic presentation in genetic and metabolic myopathies common in chronic renal failure (Muscular Dystrophy Association, 2006).

2.2.8.3 Metabolic Diseases of Muscles

Metabolic diseases of muscles are caused by different genetic defects that impair the body's metabolism. In a few metabolic muscle disorders, symptoms are not caused by a lack of energy, but rather by unused fuel molecules that build up inside muscle cells. This build-up may damage the cells, leading to chronic weakness. Changes in diet and lifestyle with an increased exercise schedule can be helpful to strengthen muscles and release energy (Muscular Dystrophy Association, 2006).

2.2.8.4 Causes of Metabolic Diseases

Metabolic diseases are caused by defects in the enzymes that control chemical reactions used to break down food. Flaws in the genes that govern production of the enzymes cause enzyme defects. Enzymes are special type of proteins that act like little machines on a microscopic assembly line, each performing a different function to break down food molecules into fuel. When one of the enzymes in the line is defective, the process goes slowly or shuts down entirely.

In normal metabolism, food provides fuel that's processed inside the cells, producing energy (ATP) for muscle contraction and other cellular functions. In metabolic myopathies, missing enzymes prevent mitochondria from properly processing fuel, and no energy is produced for muscle function (Figure 3).

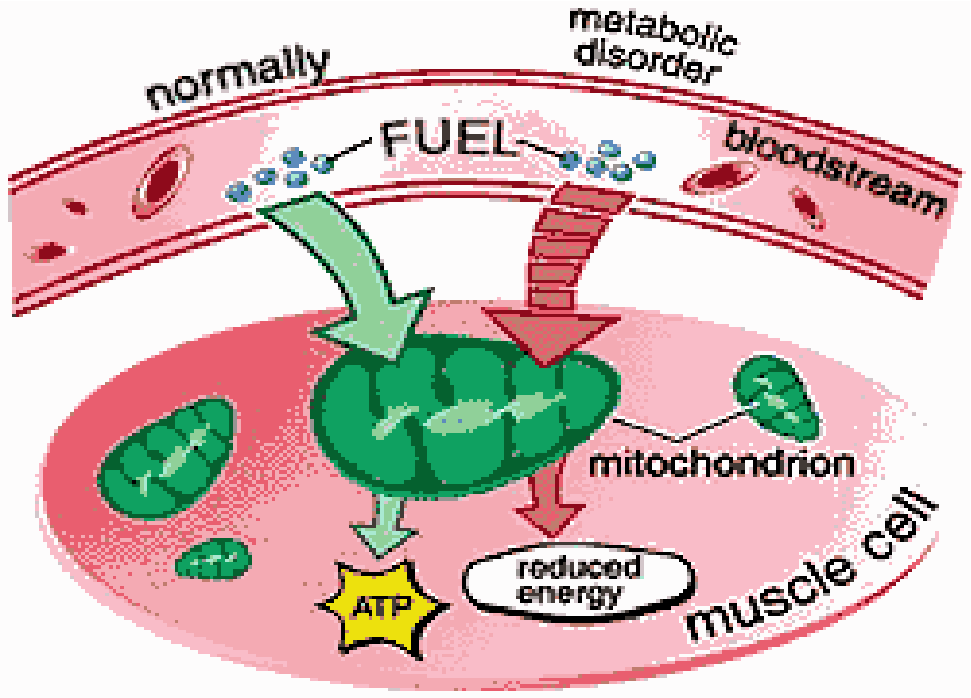

Figure 3: A muscle cell (Muscular Dystrophy Association, 2006)

Our bodies can use carbohydrates (starches and sugars), fat and protein for fuel. Defects in the cells carbohydrate and fat-processing pathways usually lead to weakness in the voluntary muscles, but may also affect the heart, kidneys or liver. Although defects in protein-processing pathways can occur as well, these usually lead to different kinds of disorders that affect other organs (Muscular Dystrophy Association, 2006).

2.2.8.5 Patients with Metabolic Disease

2.2.8.5.1 Exercise Intolerance

The main symptom of most of the metabolic myopathies is difficulty performing some type of exercise, a situation known as exercise intolerance, in which the patient becomes tired very easily. This condition is commonly found in patients with chronic renal failure. The degree of exercise intolerance in the metabolic myopathies varies greatly between disorders and even from one individual to the next within a disorder. For instance, some people may get fatigued only when jogging, while others may feel exhausted after mild exertion such as walking across a parking lot or even blow-drying the hair. Each patient must learn his activity limitations.

A person with exercise intolerance may also experience painful muscle cramps and/or injury-induced pain during or after exercising. The injury-induced pain is caused by acute muscle breakdown, a process called rhabdomyolysis. Rhabdomyolysis is painful and can cause acute renal failure. Many patients with metabolic muscle disease try to avoid triggering these episodes by modifying their physical activities and diet (Muscular Dystrophy Association, 2006).

2.2.8.5.2 Muscle Weakness

Metabolic muscle diseases characterized by exercise intolerance are not generally prone to muscle weakness. Some chronic or permanent weakness can develop in response to repeated episodes of rhabdomyolysis and to the normal loss of strength that occurs with aging and chronic renal failure. The degree of muscle weakness that develops in those disorders is extremely variable and may depend on such factors as genetic background and the number of episodes of rhabdomyolysis experienced. The diseases involving exercise intolerance do not usually progress to the degree that a wheelchair or any other mechanical assistance is needed. However, daily exercising strengthens muscles, which is recommended for patients with this condition and patients with other chronic diseases including chronic renal failure (Muscular Dystrophy Association, 2006).

2.2.9 Aim and Objective of this Study

This study aimed to ascertain whether exercise during haemodialysis has an effect on solute removal and thus reduce swelling and oedema. No such study has been conducted in Africa. Taking an idea or study from a first world country with expectedly high standards in the medical services and trying to meet the standards and guidelines of the first world country may not necessarily be easy to implement. For instance, Renal Units in first world countries have a central on-line computerized monitor which is linked to all dialysis machines in their units which is being constantly monitored by staff throughout dialysis. Thereby, correcting any problems instantly with minimum delays in providing maximum efficiency in treatment provided. Whereas in Africa, such high technology and equipment is not yet introduced and staff rectify the problem only when the dialysis machine alarms. First world countries are also better developed economically to afford to employ more staff members in their Renal Units where each staff member performs a specific duty whereas in third world countries like Africa we have few staff members performing multiple duties. This study will prove whether the Airogym is practical in this country and whether the results envisaged are achievable in this country.

The first objective of this study was to investigate if exercise during haemodialysis increases solute removal, and therefore, assist in improving the quality of haemodialysis.

The second objective was to demonstrate whether exercise during haemodialysis results in a reduction of side effects in end-stage renal disease, e.g. oedema and swelling, thereby resulting in an improvement in the quality of life for these patients.

CHAPTER THREE

MATERIALS AND METHODS

Thirty-four patients with end-stage renal failure who were on haemodialysis participated in the study. Seventeen patients were in the intervention group (aged between 25 and 60) and seventeen in the control group (aged between 18 and 60). Patients in the intervention group did not exercise for the first three months of the study in order to establish a baseline period. Thereafter, exercising took place from the fourth to the ninth month. Patients in the intervention group pedaled on an exercise cushion for fifteen minutes every hour to achieve a total of sixty minutes of exercise over a four-hour dialysis session. All patients who participated in the study were on a three times a week dialysis program. Patients in the control group did not pedal on the exercise cushion during the nine-month study period.

3.1 ETHICAL APPROVAL AND CONSENT

Patients with end-stage renal failure were recruited from two South African MediClinic Hospital Renal Units, namely, Newcastle Private Hospital Renal Unit and Bloemfontein MediClinic Renal Units. Consent was obtained from all patients who agreed to participate in the study (Appendix 1a & 1b). Ethical approval for the study was obtained from Durban University of Technology Ethics Committee.

3.2 RESEARCH DESIGN

This was a Quasi-experimental investigation, since patients participating in this research knew whether they were in the intervention group or the control group, i.e., patients in Group A were the intervention group. They were required to exercise at intervals during the haemodialysis sessions. Whereas, those in Group B, the control group, were not required to exercise during haemodialysis sessions. This was one of the limitations of this project. However, both groups were dialysed by the researcher at both renal units with the assistance of nurses

and technologists where necessary. All patients were treated the same in terms of drawing blood from them and motivating patients to maintain a good quality of life with regard to exercise, diet, joining social groups and attending psychological counseling if necessary.

Plasma concentration of urea, creatinine and potassium were measured before and after haemodialysis in both the control and intervention group. Urea Kt/V (dialysis efficiency formula) was calculated for comparison to establish efficiency. Ankle circumference was measured pre and post haemodialysis to establish whether there was any improvement in pedal oedema. The results of the intervention group (patients exercising) were compared to the results of the control group (patients not exercising during haemodialysis). Dialysate flow rates, dialysers and treatment time were the same for all patients.

Informed consent was obtained from all patients who participated in the study and patient's confidentiality was maintained.

3.2.1 Sample Size

A sample size of thirty-four patients with chronic renal failure on a haemodialysis program was recruited to participate in this study over a nine-month period. Fourteen patients were recruited from Newcastle Private Hospital Renal Unit and twenty patients from Bloemfontein MediClinic Renal Unit. These two units were selected because the investigator was employed as a clinical technologist in both the units. The reason for selecting thirty-four patients is due to the small number of patients attending haemodialysis in both the hospitals i.e. the average number of patients on the chronic dialysis program in Bloemfontein per month is thirty and twenty in Newcastle. Twenty-eight patients successfully completed this experiment i.e. fourteen patients in each group. This sample size of twenty-eight was sufficient for statistical analysis in this investigation because patients exercised three times a week over a six month period. Sufficient data was

gathered for the analysis. A clinical examination was conducted on all patients before selecting them to participate in the study. Patients had to meet the selection criteria in order to participate in the study.

3.2.2 Sampling Procedure

Only patients who met all the inclusion criteria, listed below, were recruited for the study:

3.2.2.1 Inclusion Criteria

All patients had to comply with the following:

- On a chronic haemodialysis schedule
- Haemodynamically stable
- Attended haemodialysis at the Bloemfontein MediClinic Hospital or Newcastle Private Hospital Renal Unit
- Received haemodialysis three times a week
- Eighteen years old and above
- Of any sex (male or female)
- Of any race
- No contraindication to exercise on dialysis (decided by the patients' treating physician)

3.2.2.2 Exclusion Criteria

The following patients were excluded from the study:

- Those not on a chronic haemodialysis schedule
- Those medically unfit to participate (confirmed by consulting Doctors).
- Those not willing to comply with protocol
- Diabetic patients.

3.2.3 Sample Allocation

Random allocation was utilized to assign the patients who met the inclusion criteria to their respective groups, with the patients drawing a letter (A or B) out of an envelope. A total of twenty patients were recruited from Bloemfontein (ten in group A and ten in group B) and fourteen from Newcastle (seven in group A and seven in group B).

3.2.4 Specimen Collection

Pre and post haemodialysis blood samples were drawn from each patient, monthly, over the nine month period. The blood samples were drawn from the haemodialysis bloodlines.

Procedure

Venous whole blood (5ml) was obtained from patients in the intervention group and in the control group. Blood sample tubes and vacutainer needles (sterile) were used to draw blood directly from the arterial port of the arterial bloodlines, which forms part of the extracorporeal circuit during haemodialysis (Figure 4). Pre-haemodialysis blood samples were drawn as soon as patients commenced dialysis to prevent the sample from reflecting any impact of dialysis. These factors included:

- presence of saline in the blood lines
- presence of heparin in the blood lines
- diffusion and ultrafiltration

Post haemodialysis blood samples were drawn using a slow flow pump technique that prevents sample dilution with recirculation blood and minimizes the confounding effects of urea rebound. After blood samples were taken they

were sent immediately to the pathology laboratory for measurements of urea, creatinine and potassium.

Figure 4: Patient on Haemodialysis, showing the Extracorporeal Circuit (Photographed in the unit).

3.2.5 Procedure during Dialysis

During the first three months of this research patients in the intervention group did not exercise on the exercise cushion to establish a baseline. Thereafter, from the fourth month until the ninth month patients in the intervention group pedaled on the exercise cushion during haemodialysis (Table 2). These patients pedaled for fifteen minutes every hour over the four- hour haemodialysis session. During these fifteen minutes all patients exercised at a slow steady rate to target a heart rate of 100 beats per minutes and then slowed down gradually. A total of sixty minutes of exercise was performed over the four hours on haemodialysis. Patient's ankle diameter just above the level of the lateral malleolus were

measured using a tape measure before and after haemodialysis to measure changes in the ankle circumference in order to establish whether there was an improvement in oedema.

Table 2: Timeframe allocated to the Exercise Procedure during the Nine-month Study Period

Months	Intervention group (Group A)	Control group (Group B)
1	No exercise during dialysis	No exercise during dialysis
2	No exercise during dialysis	No exercise during dialysis
3	No exercise during dialysis	No exercise during dialysis
4	Exercising during dialysis	No exercise during dialysis
5	Exercising during dialysis	No exercise during dialysis
6	Exercising during dialysis	No exercise during dialysis
7	Exercising during dialysis	No exercise during dialysis
8	Exercising during dialysis	No exercise during dialysis
9	Exercising during dialysis	No exercise during dialysis

3.3 EXPERIMENTAL APPARATUS

3.3.1 The Airogym Cushion

The Airogym cushion (manufactured by Airogym SA) is an inflatable device designed to address problems of ankle swelling and blood clotting (Figure 5). It is assembled by inflating the cushion orally and sealing the inflation port with a rubber stopper attached to the cushion. After inflation and sealing the opening for inflation the exercise cushion is ready for use. By squeezing the foot alternately against the cushion i.e. when the right foot squeezes the cushion in, the left foot relaxes and vice-versa. By pressing down on the footpad, the veins in the foot are compressed, squeezing blood flow into the main veins in the calf. The pressure involved in squeezing the foot causes muscular contractions of the calf muscles promoting the flow of blood through the main veins. This prevents venous stasis and reduces the risk of ankle swelling. It is a very gentle and non-aggressive form of exercise, which is ideally suited for patients on haemodialysis who sit in the same position for four hours with restricted movements while being seated. Airogym was designed for passengers flying in an airoplane on long haul flights (Scurr and Perry, 2001). In long haul flights passengers are at risk of developing thrombosis and oedema because of venous stasis.

Figure 5: Patient pedaling on the Airogym Cushion during Haemodialysis (Photographed in Renal Unit).

3.3.2 Measurement of Oedema.

Oedema of the lower limb was evaluated by measuring the diameter around the ankles both before and after dialysis. The difference enabled us to determine whether exercising during haemodialysis caused a further reduction in oedema apart from the efficiency of the haemodialysis treatment.

3.3.3 The Haemodialysis Machine

The haemodialysis machine which was used to dialyse all the patients recruited in this research was the B Braun Dialog machine with the software version 3.4 and 6.2. Haemodialysis was performed using the standard procedure, whereby blood was routed out of the patients body via their venous access by the blood pump on the haemodialysis machine. The blood passess through the bloodlines into the dialyser were diffusion and ultrafiltration occurs and is then returned to the patient.

3.3.4 Measurement of Urea, Creatinine and Potassium

Creatinine

The Abbot Architech C800 was used to measure the creatinine levels in the blood, the method used to measure the creatinine levels was the Alkaline Picrate method (Kinetic Jaffe Method). The principle of the technique is as follows:

$$\text{Sample + Picrate} \xrightarrow{\text{Alkaline pH}} \text{Creatinine Picrate Complex}$$

The serum sample is mixed with alkaline Picrate to form the creatinine picrate complex and the rate of change in absorbance is measured. The rate of absorption of Alkaline increases at 500 nm wave length due to the formation of

this complex. The Creatinine Picrate Complex is directly proportional to the concentration of creatinine in the sample (Bishop, Fody and Schoeff, 2005).

Blood Urea Nitrogen

The machine used for testing the urea levels was the Abbot Architech C800. The method used to measure the urea levels was the Urease method **(**Sampson and Baird, 1979). The assay is a modification of a totally enzymatic procedure. The test is performed as a kinetic assay in which the initial rate of the reaction is linear for a limited period of time. Urea in the sample is hydrolysed by urease to ammonia and carbon dioxide. Ammonia is then catalysed by glutamate dehydrogenase (GLD) producing glutonate and water with the concurrent oxidation of Nicotinamide Adenine Dinucleotide (NADH). Two milliliters of NADH is oxidized for each molecule of urea present. The initial rate of decrease in absorption at 340nm is proportional to the urea concentration in the sample.

Potassium

The method used to measure the potassium levels was the Ion Selective Electrode method (http://www.nico2000.net/analytical/potassium.htm). Ion selective electrodes for Sodium, Potassium and Chloride utilize membrane selective to each of these ions. An electric potential is developed across the membranes between the reference and measuring electrodes in accordance with the Nernst equation. The voltage is compared to previously determined calibrated voltage and converted into ion concentration.

3.4 STATISTICAL ANALYSIS

Statistical analysis was carried out with the use of the Stata computer programme and reviewed by a statistician. Results are represented as the mean and standard deviation. Significance was calculated by a parametric test. Paired

student’s t-test was used to determine level of significance. P-values< 0.05 were taken to be statistically significant.

CHAPTER FOUR

RESULTS

The effect of exercise on solute removal and oedema during haemodialysis in end-stage renal disease is represented by graphs and tables. Thirty-four patients with end-stage renal disease were recruited in the study. However, twenty-eight patients successfully completed this experiment i.e. fourteen patients in the intervention group and fourteen patients in the control group. In consultation with the statistician, this sample size of twenty eight was found to be sufficient for statistical analysis as this study was done over a nine month period. Patients in the intervention group exercised three times per week, for six months and sufficient data was gathered for analysis. In the intervention group two patients had passed away during the study period. The third patient withdrew from the study due to the fact that he experienced hypotension during haemodialysis. In the control group one patient passed away during the study period. The other two patients had poor venous accesses and went on to Peritoneal Dialysis.

The first three months of the study i.e. January to March is the baseline period. No patients exercised during this period. Patients in the Intervention Group (Group A), commenced exercise at the beginning of April and continued until the end of September, i.e. for six months. Patients exercised for fifteen minutes every hour to achieve sixty minutes of exercise over the four hour haemodialysis treatment. Patients in the control group (Group B) did not exercise during the study period. The measurement of blood urea, creatinine and potassium was determined at the end of each month. Therefore, the results shown in April (Table 3) were taken after the first month of exercising. Significant changes in the solute levels and oedema are indicated by P values were $P<0.05$ indicates a significant change and $P> 0.05$ indicates no significance.

4.1 The effect of Exercise during Haemodialysis on Serum Urea Levels

The pre and post haemodialysis mean serum urea values ± standard deviation (SD) in the intervention and control groups over the nine month period are represented in Table 3 below.

Table 3: Pre and post Haemodialysis Mean Serum Urea Values ± SD (mmol/L) in the Intervention and Control Groups over Nine Months

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
Intervention Pre	29.9±8.2	31.0±8.4	31.4±8.1	29.1±8.0	29.6±7.3	30.4±8.5	29.9±7.7	30.9±8.5	29.5±10.3
Control Pre	31.2±9.5	31±8.2	30.7±10.3	30.4±9.3	30.9±8.1	32.6±6.9	31.6±8.1	30.8±9.3	34.4±9.6
Intervention Post	8.3±2.6	8.3±2.5	8.6±2.7	7.1±2.1	6.7±2.0	6.3±1.6	6.0±2.0	5.7±2.1	5.0±1.9
Control Post	7.9±2.0	8.3±1.5	7.9±2.1	8.1±2.0	7.7±1.9	8.2±0.8	8.0±1.8	8.1±2.1	8.9±2.0

4.1.1 Pre Haemodialysis Mean Serum Urea Levels in the Intervention Group

The mean serum urea values and SD at baseline were 29.9 ± 8.2 mmol/L (Jan), 31.0 ± 8.4 mmol/L (Feb) and 31.4 ± 8.1 mmol/L (March) (Table 3). This suggests that there were no significant changes in the serum urea level at baseline (p= 0.4), (Figure 6).

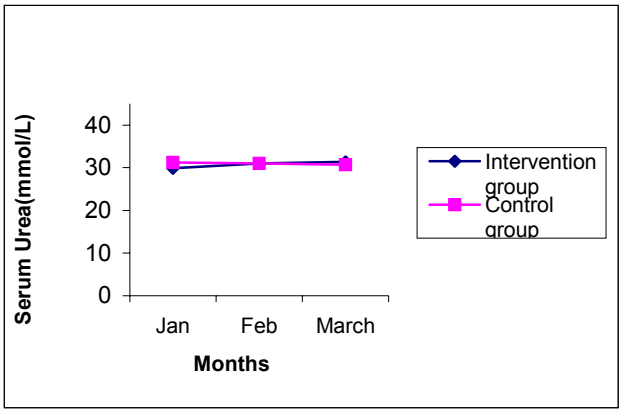

Figure 6: Pre Haemodialysis Mean Serum Urea Levels at Baseline.

From April to September (exercise period) the serum urea means values and standard deviation was 29.1 ± 8.0 mmol/L in April (at commencement) and 29.5 ± 10.3 mmol/L in September (after six months of exercising), (Figure 7). There was therefore no significant difference observed in the serum urea levels in the intervention group over time (p = 0.5).

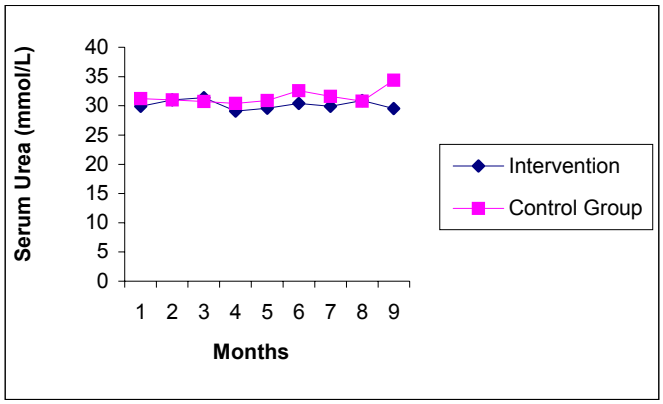

Figure 7: Pre Haemodialysis Mean Serum Urea Levels in the Intervention and Control Groups over Nine Months

4.1.2. Pre Haemodialysis Mean Serum Urea Levels in the Control Group

The mean values and SD at baseline were 31.2 ± 9.5 mmol/L (Jan), 31 ± 8.2 mmol/L (Feb), 30.7 ± 10.3 mmol/L (March), (Table 3). These values indicate that there were no significant changes in the serum urea levels at baseline in the control group (p = 0.9). From April to August the mean serum urea levels showed no significant changes with April 30.4 ± 9.3 mmol/L and August 30.8 ± 9.3 mmol/L (p = 0.6). For the month of September there was an increase in the mean value and SD of serum urea compared to the previous months. The mean value and standard deviation of mean serum urea levels in September was 34.4 ± 9.6 mmol/L compared to April which was 30.4 ± 9.3 mmol/L. This increase in mean serum urea for one month only had no significant impact on the overall study period.

4.1.3. Comparison between Pre Haemodialysis Mean Serum Urea Levels in the Intervention and Control Groups

The mean serum urea levels pre haemodialysis showed no significance between the two groups over the study period (p = 0.9). Figure 6 shows the mean values plotted on the figure are flowing along the same gridline at baseline. From April to August there were no significant differences between the two groups (p = 0.7), (Figure 7, Table 3). From August to September there was a significant difference between the two groups. However, the difference in serum urea between the two groups for September had no significant effect on the overall study period.

4.1.4. Post haemodialysis Mean Serum Urea Levels in Intervention Group

The serum urea levels in the Intervention group at baseline remained constant. The mean values and standard deviations in January was 8.3 ± 2.6 mmol/L, February 8.3 ± 2.5 mmol/L, and March 8.6 ± 2.7 mmol/L (Table 3). Although there was a slight rise in the serum urea mean value in March, it was not significant over the overall baseline period (p = 0.6) (Figure 8).

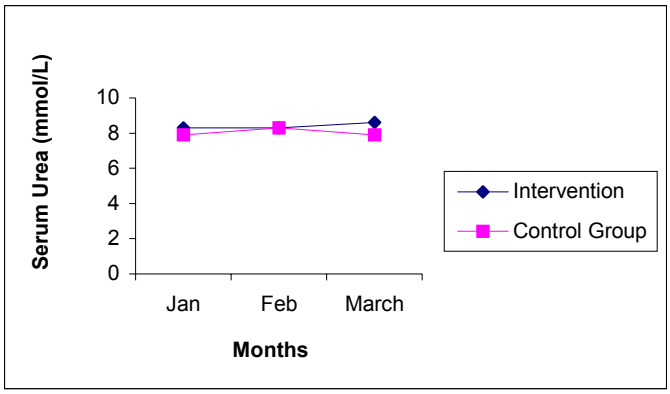

Figure 8: Post Haemodialysis Mean Serum Urea Levels at Baseline.

From April to September (the exercise period), the mean serum urea levels showed a significant reduction. The mean value and SD on commencement of

exercise in April, was 7.1 ± 2.1 mmol/L (Table 3). In September, the end of the six months exercise period, the mean serum urea levels dropped to 5.0 ± 1.9 mmol/L. Figure 9 shows a decreased in the serum urea levels in the intervention group over the exercise period. There was a significant reduction in the mean serum urea levels by 30% between April and September ($p<0.001$). This suggests that exercise during haemodialysis improves urea clearance by 30% over a six-month period.

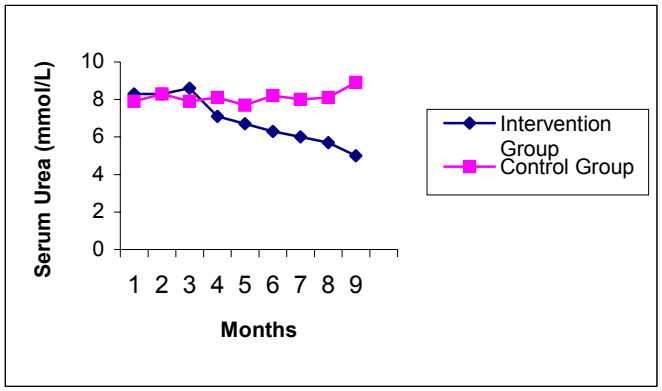

Figure 9: Post Haemodialysis Mean Serum Urea Levels in the Intervention and Control Groups over Nine Months ($p<0.001$).

4.1.5 Post Haemodialyis Mean Serum Urea Levels in the Control Group

The mean values and SD for January were 7.9 ± 2.0 mmol/L, February 8.3 ± 1.5 mmol/L, and March 7.9 ± 2.1 mmol/L which showed no significant difference over the three months even though there was an increase in the mean value in February compared to January and March ($p = 0.6$) (Table 3). From April to August the serum urea mean values and SD were constant with April 8.1 ± 2.0 mmol/L at the commencement of exercise compared to August 8.1 ± 2.1 mmol/L (Figure 9). In September there was an increase in the serum urea mean value, 8.9 ± 2.0 mmol/L compared to the previous months. However, this showed no significance over the overall study period, ($p = 0.2$).

4.1.6 Comparison of Mean Serum Urea Levels between the Intervention and Control Groups Post Haemodialysis

The serum urea levels at baseline showed no significant difference between the two groups ($p = 0.6$) (Figure 8). From April to September there was a significance difference between the two groups ($p<0.001$) (Figure 9). The mean serum urea values in the control group followed a constant flow whereas the intervention group showed a decline in the graph over the exercise period.

4.1.7 Comparison between the Pre and Post Mean Serum Urea Levels in the Intervention Group

In the intervention group the pre haemodialysis serum urea levels remained constant at baseline showing no significance ($p = 0.4$), (Table 3). The post haemodialysis mean serum urea levels also remained constant at baseline ($p = 0.6$). However there was a significant difference between the pre and post mean serum urea levels at baseline ($p<0.001$) (Figure 10). From April to September the pre mean serum urea levels in the intervention group showed no significant differences ($p = 0.5$). The pre haemodialysis serum urea values plotted on the figure from April to September followed a constant flow. The post mean serum urea mean values showed a significant decrease from April to September (Table 3). There was a significant reduction of 30% in the mean serum urea levels from the point of intervention until the end of the study period ($p<0.001$) (Figure 10).

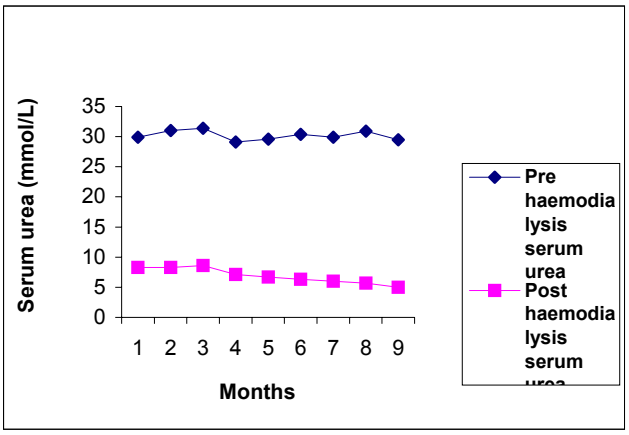

Figure 10: Pre and Post Haemodialysis Mean Serum Urea Levels in the Intervention Group (p<0.001).

4.1.8 Comparison between Pre and Post Haemodialysis Mean Serum Urea Levels in the Control Group

The pre haemodialysis levels in the control group at baseline showed no significant differences (p = 0.9), (Figure 11). The post haemodialysis mean serum urea levels at baseline also showed no significant differences (p = 0.6). There was therefore no significant difference between the pre and post serum urea levels at baseline (Table 3). From April to September the pre haemodialysis mean serum urea levels also showed no significance (p = 0.6). From April to September the post haemodialysis mean serum urea levels followed a constant flow (Figure 11) showing no significance in the control group (p = 0.2). There was therefore no significant difference between the pre and post mean serum urea levels in the control group from baseline throughout the study period (p = 0.9).

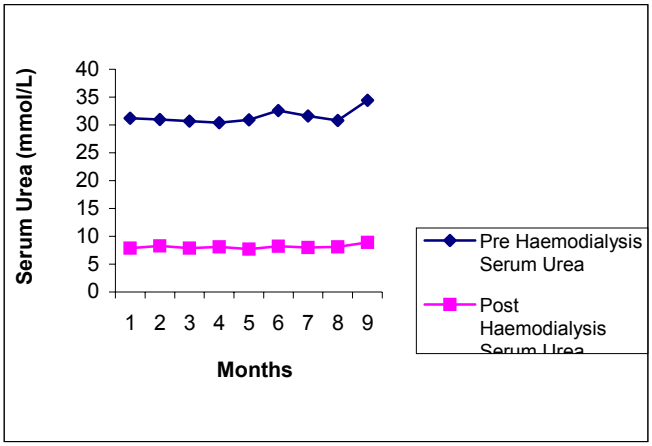

Figure 11: Pre and Post Haemodialysis Mean Serum Urea Levels In the Control Group.

4.2. The Effect of Exercise during Haemodialysis on Serum Creatinine

The pre and post haemodialysis mean serum creatinine values ± SD in the intervention and control groups over the nine month period are represented in Table 4 below.

Table 4: Pre and Post Haemodialysis Creatinine Mean Values ± SD (µmol/L) in the Intervention and Control Groups over Nine Months

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
InterventionPre	1162±357	1109±312	1053±272	914±201	859±194	787±227	798±179	793±175	796±175
Control Pre	961±312	870±388	921±293	956±337	945±325	948±294	993±338	966±302	895±381
InterventionPost	627±218	560±148	521±133	452±122	418±123	369±108	342±94	341±91	340±92
Control Post	428±142	398±144	409±154	433±152	386±136	422±155	453±195	419±125	397±165

4.2.1. Pre Haemodialysis Creatinine Clearance in the Intervention Group

The creatinine mean values and SD for January (1162 ± 357 µmol/L), February (1109 ± 312 µmol/L) and March (1053 ± 272µmol/L) showed a significant decrease ($p = 0.007$) (Figure 12).

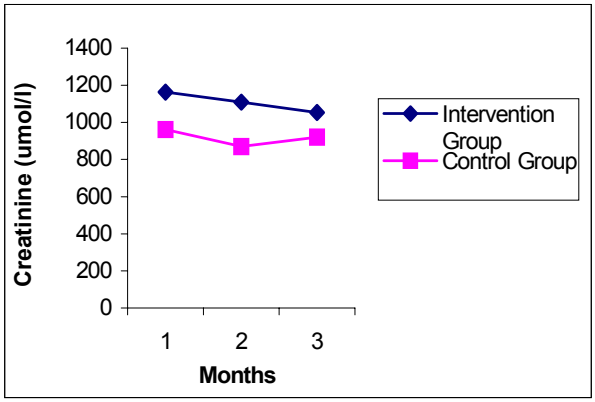

Figure 12: Pre Haemodialysis Mean Creatinine Levels in the Intervention and Control Groups at Baseline (p= 0.007).

From April to June there was a reduction in creatinine levels pre haemodialysis (Table 4). The creatinine mean value and SD in April (after the first month of exercising) was 914.4 ± 200.5 µmol/L, May 859.3 ± 193.6 µmol/L and June 787.4 ± 227.3 µmol/L ($p<0.001$). This suggests that exercise during haemodialysis had an effect on pre haemodialysis creatinine levels from April to June. From July (798 ± 179 µmol/L) to September (796 ± 175 µmol/L) the creatinine mean values and SD showed no significance in creatinine clearance ($p = 0.9$) (Figure 13).

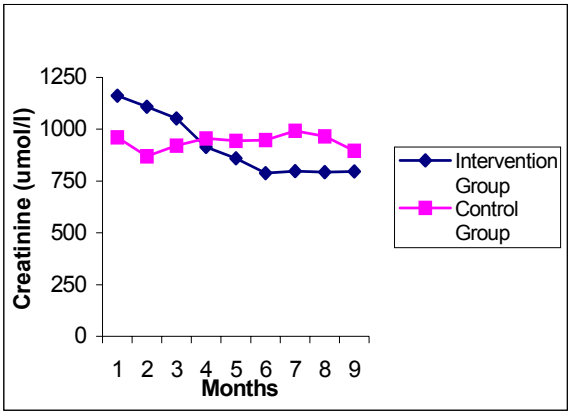

Figure 13: Pre Haemodialysis Mean Creatinine Levels over the Nine-month Study Period in the Intervention and Control Groups (p<0.001).

4.2.2. Pre Haemodialysis Creatinine Clearance in the Control Group

The creatinine mean values for January (961 ± 312 µmol/L), February (870 ± 388 µmol/L) and March (921 ± 293 µmol/L) showed no significant differences (p = 0.3). From April (956 ± 337 µmol/L) to September (895 ± 381 µmol/L) the creatinine mean values and SD showed no significance (Table 4). There was therefore no significant changes in creatinine clearance in the control group over the study period (p = 0.6).

4.2.3. Comparison between the Pre Haemodialysis Creatinine Clearance in the Intervention and Control Groups

The creatinine levels at baseline showed no significant difference between the two groups (p = 0.10). From April to September there were no significant differences between the intervention and control group (p = 0.4).

4.2.4 Post haemodialysis mean creatinine levels in the Intervention Group

The post creatinine mean values at baseline started at 626.9 µmol/L in January and dropped to 520.6 µmol/L in March (Table 4). There was a significant reduction in mean creatinine levels at baseline post haemodialysis in the intervention group (p = 0.01) (Figure 14).

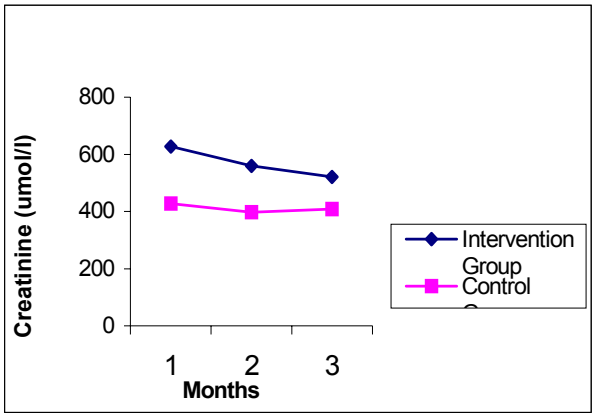

Figure 14: Post Haemodialysis Mean Creatinine Levels In the Intervention and Control Groups at Baseline (p = 0.01).

From April to June the creatinine clearance improved and creatinine mean value reduced from 451.7 µmol/L in April to 369.1 µmol/L in June. This was a significant reduction in creatinine levels post haemodialysis ($p<0.001$). This suggests that exercise during haemodialysis reduced creatinine levels for three months. From July to September the mean creatinine levels remained constant from July (342.1 µmol/L) to September (339.6 µmol/L) showing no significant difference ($p > 0.45$) (Figure 15).

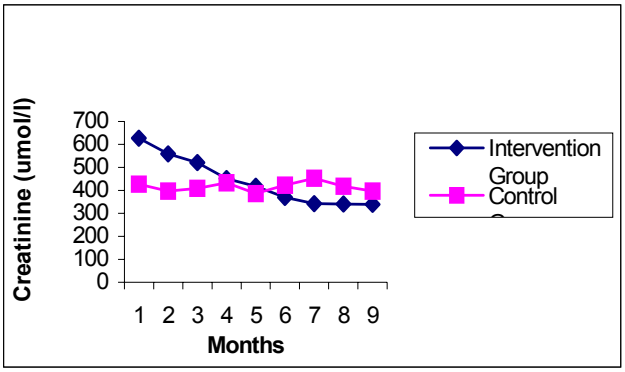

Figure 15: Post Haemodialysis Mean Creatinine Levels over Nine-Months In the Intervention and Control groups ($p<0.001$).

4.2.5 Post Haemodialysis Creatinine Levels in the Control Group

The creatinine mean values and SD in January was 427.6± 141.8 µmol/L, February 397.7 ± 144.2 µmol/L and March 408.6 ± 154.4 µmol/L (Table 4). There were no significant changes in creatinine mean values at baseline in the control group ($p = 0.1$). From April to September the creatinine mean values in the control group fluctuated slightly but was of no statistical significance ($p = 0.9$), (Figure 15).

4.2.6 Comparison between the Post Haemodialysis Creatinine Levels in the Intervention and Control Groups:

The creatinine mean levels at baseline between the two groups showed a significant difference ($p = 0.005$). In the intervention group the mean creatinine levels started at 626.9 µmol/L and was reduced to 520.6 µmol/L in March whereas the mean creatinine levels in the control group started at 427.6 µmol/L in January and reduced to 408.6 µmol/L in March (Figure 14). This suggests that more creatinine was cleared by haemodialysis in the intervention group at baseline than the control group. After the baseline period the creatinine mean levels in the control group showed no significance over the study period, April (428 ± 142 µmol/L) to September (397 ± 165 µmol/L), ($p = 0.9$). The creatinine mean values in the intervention group dropped significantly from April (452 ± 122 µmol/L to July (342 ± 94 µmol/L) ($p<0.001$).There was a statistically significant difference between the two groups from April to July ($p = 0.01$). From July to September the creatinine mean levels in the intervention group and the control group remained constant with no significant changes between the two groups ($p = 0.09$). The creatinine levels in the intervention group compared to the control group started at 626 ± 218.4 µmol/L in January and reduced to 339.6 ± 92.2 µmol/L in September which was a 46% reduction at the end of the nine months compared to the control group were the creatinine levels started at 427.6 ± 141.8 µmol/L and reduced to 397.0 ± 165.1 µmol/L, which was a 7% reduction post haemodialysis (Table 4).

4.2.7 Comparison between Pre and Post Creatinine Levels in the Intervention Group

The pre and post haemodialysis creatinine levels dropped over the study period. At baseline the difference between the creatinine levels pre and post was greater than the difference between creatinine levels at the end of the study i.e. the

mean creatinine levels in January started at 1162.2 µmol/L pre haemodialysis and dropped to 626.9 µmol/L post haemodialysis with a difference of 535.3 µmol/L. The creatinine levels in September was 796.9 µmol/L pre haemodialysis and 339.6 µmol/L post haemodialysis with a smaller difference of 457.3 µmol/L compared to January of 535.3 µmol/L . Therefore as the pre and post creatinine mean values reduced over time the creatinine clearances decreased over time. In the Intervention group the haemodialysis mean creatinine clearance at baseline was 9% pre haemodialysis and 17% post haemodialysis. From April to June the creatinine clearance was 14% pre haemodialysis and 18% post haemodialysis. From July to September the creatinine clearance was 0% pre haemodialysis and 1% post haemodialysis. The most amount of creatinine clearance took place between April and June post haemodialysis in the intervention group.

4.2.8 Comparison between Pre and Post Creatinine levels in the Control Group

The pre haemodialysis creatinine levels started at 960.8 µmol/L in January, 956.4 µmol/L in April and 966.2 µmol/L in August indicating no significant changes. The post haemodialysis creatinine levels started at 427.6 µmol/L in January, 433.2 µmol/L in April and 418.8 µmol/L in August indicating no significant changes. The difference between the pre and post creatinine mean values showed a significant drop in creatinine levels between the two (Table 4). There was a significant decrease in creatinine levels post haemodialysis compared to pre haemodialysis ($p < 0.001$).

4.3 The Effect of Exercise during Haemodialysis on Urea Kt/V

The Kt/V formula (page 11) was used to determine the efficiency of dialysis by reducing urea levels. According to the National Kidney Foundation (NKF),

Dialysis Outcomes Quality Initiative (DOQI) guidelines, the minimum prescribed dose of haemodialysis should be a Kt/V of 1.2.

4.3.1 Mean Serum Urea Kt/V in the Intervention Group

The mean serum urea Kt/V in the intervention group at baseline remained constant (Table 5). The mean serum urea Kt/V values and SD were 1.2 ± 0.14 in January, 1.2 ± 0.13 in February, and 1.2 ± 0.14 in March indicating no change. Therefore there were no significant changes in Kt/V at baseline (P = 0.2). In April, after the first month of exercising the mean serum urea Kt/V value increased to 1.3. In June there was another increase in mean serum urea Kt/V value to 1.4. Thereafter the serum urea Kt/V values maintained a constant level until September. The serum urea Kt/V mean values increased from 1.2 at baseline to 1.4 in September after six months of exercising. This was a 17% increase in serum urea Kt/V after six months of exercising (p = 0.5).

Table 5: Mean Serum Urea Kt/V mean and SD in the Intervention and Control Groups

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
Intervention	1.2 ± 0.14	1.2± 0.13	1.2± 0.14	1.3± 0.13	1.3± 0.12	1.4± 0.10	1.4± 0.11	1.4± 0.12	1.4± 0.12
Control	1.2± 0.16	1.2± 0.16	1.3± 0.13	1.2± 0.13	1.3± 0.13	1.3± 0.12	1.3± 0.13	1.2± 0.13	1.3± 0.13

4.3.2 Mean Serum Urea Kt/V in the Control Group

The serum urea Kt/V in the control group at baseline remained constant (Table 5). The serum urea Kt/V mean values and SD was 1.2 ± 0.16 in January, 1.2 ± 0.16 in February and 1.2 ± 0.13 in March (p = 0.6). These mean serum urea Kt/V values indicate consistency at baseline.

There were no changes in the serum urea Kt/V mean value in April compared to the baseline values. In May and June the serum urea Kt/V mean values increased to 1.3 and then dropped in July and thereafter remained at 1.3 in August and September. The increase in serum urea Kt/V from January to September was 8% (p = 0.4) (Figure 16).

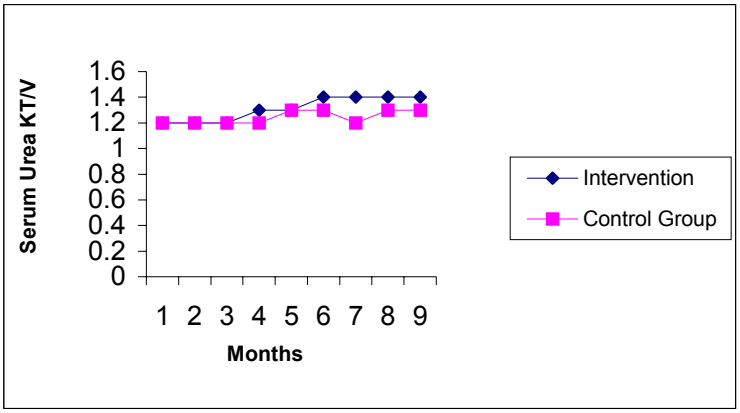

Figure 16: Mean Serum Urea Kt/V Values

4.3.3 Differences between Serum Urea Kt/V in Intervention and Control Groups

The differences in the mean serum urea Kt/V between the intervention and control groups at baseline showed no statistical significance (p = 0.3), (Figure 16). From April to September the mean serum urea Kt/V for both the intervention and control groups had raised serum urea Kt/V values for the intervention group above the control group. The difference between the two groups was statistically significant (p < 0.001) between January and September. The serum urea Kt/V mean values in the intervention group improved by 17% and the control group by 8% indicating a 9% greater improvement in mean urea Kt/V in the intervention group than the control group.

4.4 The Effect of Exercise During Haemodialysis on Potassium

4.4.1 Pre Haemodialysis Potassium Clearance in the Intervention Group

The potassium levels at baseline in the intervention group remained constant. In Table 6 the potassium mean values and S D at baseline were 5.5 ± 1.0 mmol/L in January, 5.0 ± 0.9 mmol/L in February and 5.1 ± 1.1 mmol/L in March, showing no significant differences.

Table 6: Pre and Post Haemodialysis Potassium (mmol/L) mean values and S D in the Intervention and Control Groups

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
Intervention pre	5.5±1.0	5.0±0.9	5.1±1.1	5.3±1.0	4.9±1.0	4.8±0.9	5.0±1.0	5.0±0.9	5.0±0.7
Control pre	5.2±0.8	4.9±0.7	5.1±1.0	5.0±0.7	5.1±0.6	4.9±0.6	5.0±0.7	4.8±0.4	4.6±0.4
Intervention post	4.2±0.7	3.8±0.4	3.9±0.7	4.0±0.6	3.6±0.8	3.7±0.6	3.9±0.6	3.8±0.4	3.7±0.5
Control post	3.8±0.3	3.6±0.3	3.7±0.5	3.8±0.3	3.5±0.4	3.6±0.2	3.7±0.4	3.6±0.1	3.5±0.2

In Figure 17 the potassium mean values plotted at baseline indicated no significance, p = 0.2. From April to September the potassium mean values and SD were approximately the same, i.e., in April 5.3 ± 1.0 mmol/L compared to September, 5.0 ± 0.7 mmol/L. There were no significant differences in the potassium levels pre haemodialysis in the intervention group over the study period (p = 0.09).

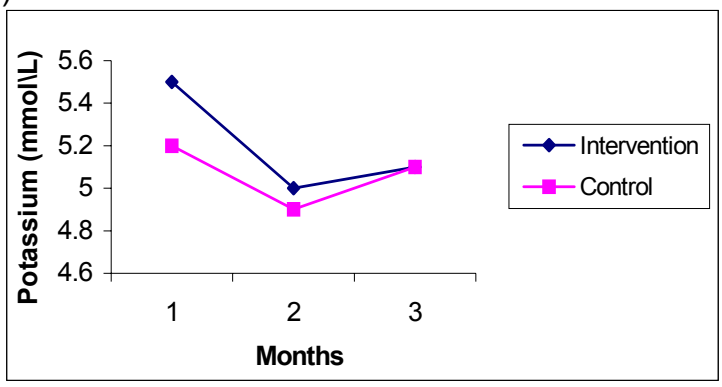

Figure 17: Pre Haemodialysis Potassium Levels at Baseline in the Intervention and Control Groups

4.4.2 Pre Haemodialysis Potassium Clearance in the Control Group

The potassium mean values at baseline in the control group remained constant. In Table 6, the potassium mean values and SD at baseline were 5.2 ± 0.8 mmol/L in January, 4.9 ± 0.7 mmol/L in February and 5.1 ± 1.0 in March showing no significant differences. In Figure 17, the potassium mean values plotted at baseline followed a straight path indicating no significance, p = 0.4. From April to July the potassium mean values and SD were constant indicating no significance (P = 0.4). From August to September the potassium mean values and SD dropped. In August it was 4.8 ± 0.4 mmol/L as compared to July when it was 5.0 ± 0.7 mmol/L. The potassium mean values and SD dropped further in September to 4.6 ± 0.4 mmol/L, (p = 0.05), which was of no significance.

4.4.3 Comparison between the Pre Haemodialysis Potassium Levels in the Intervention and Control Groups

The potassium levels between the two groups at baseline showed no significant differences, p = 0.6. The potassium mean values followed the same pattern from April to July (Figure 18), where p = 0.9, and from August to September (p = 0.4), indicating no significant differences between the two groups.

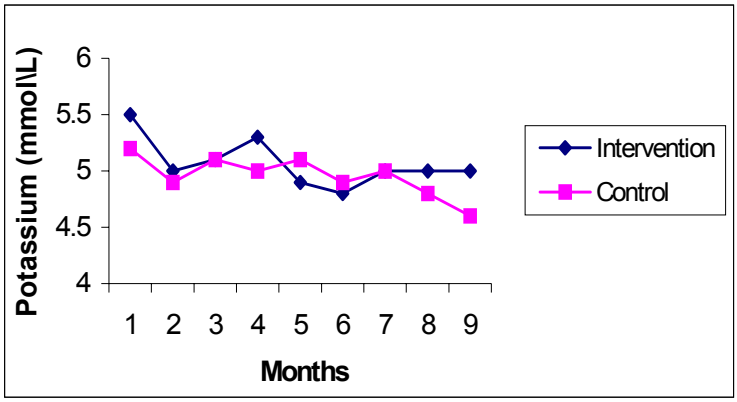

Figure 18: Pre Haemodialysis Potassium Levels in the Intervention and Control Groups over the Study Period

4.4.4 Post haemodialysis potassium levels in the Intervention Group

The post haemodialysis potassium mean values in the intervention group at baseline showed no significant differences (p = 0.23). In Table 6, the potassium mean values and SD between January (4.2 ±0.7 mmol/L), February (3.8 ± 0.4 mmol/L) and March (3.9 ± 0.7 mmol/L) fluctuated, but was of no significance (p = 0.23). From April to September the potassium mean value were reduced from 4.0 mmol/L in April to 3.7 mmol/L in September. There was an 8 % reduction in potassium levels between April and September post haemodialysis in the intervention group (p = 0.2).

4.4.5 Post haemodialysis potassium levels in the Control Group

The potassium levels in the control group at baseline fluctuated between January and February and between February and March. However, they were of no statistical significance, p = 0.4 (Figure 19).

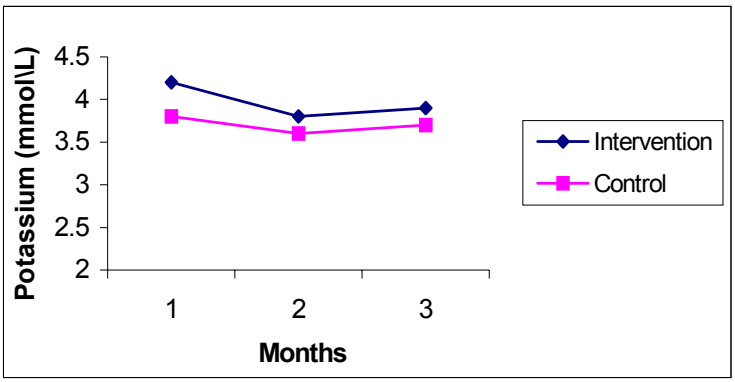

Figure 19: Post Haemodialysis Potassium Levels in the Intervention and Control Groups at Baseline

From April to September there were no significant differences in the potassium mean levels in the control group (p = 0.126).

4.4.6 Comparison between Post Haemodialysis Potassium levels in the Intervention and Control Groups

The potassium mean values between the intervention and control groups at baseline showed no statistical significance, p = 0.06 (Figure 19). From April to September the differences between the two groups showed no statistical significance (p = 0.7) (Figure 20).

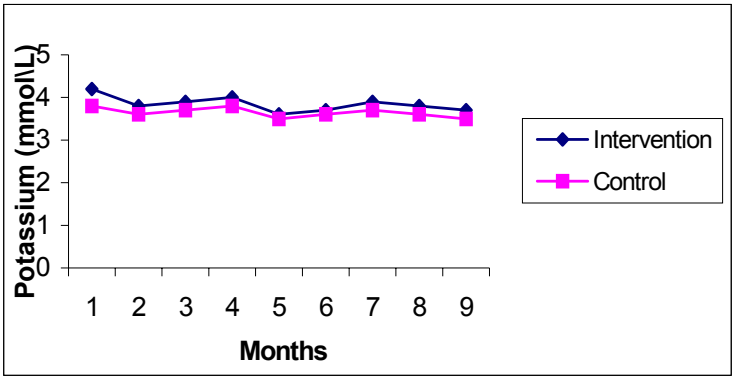

Figure 20: Post Haemodialysis Potassium Levels in the Intervention and Control Group

4.4.7 Comparison between pre and post potassium levels in the Intervention Group:

In the Intervention group the pre haemodialysis potassium levels at baseline ranged between 5 mmol/L and 5.5 mmol/L and were reduced to between 3.8 mmol/L and 4.2 mmol/L. This reduction in potassium post haemodialysis was statistically significant (p < 0.001)(Figure 21).

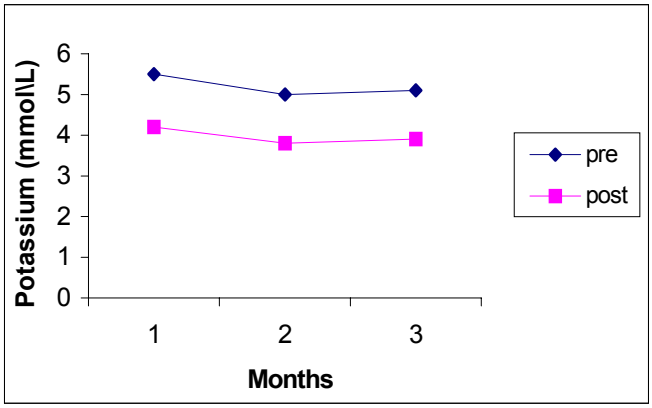

Figure 21: Pre and Post Haemodialysis Potassium Levels at Baseline in the Intervention group (p<0.001)

From April to September the potassium levels pre haemodialysis ranged between 3.8 mmol/l and 5.3 mmol/l and was reduced post haemodialysis to between 3.6 mmol/l and 4 mmol/l. This reduction in potassium post haemodialysis was statistically significant ($p < 0.001$)(Figure 22). However the reduction in potassium levels post haemodialysis at baseline was almost the same reduction throughout the study.

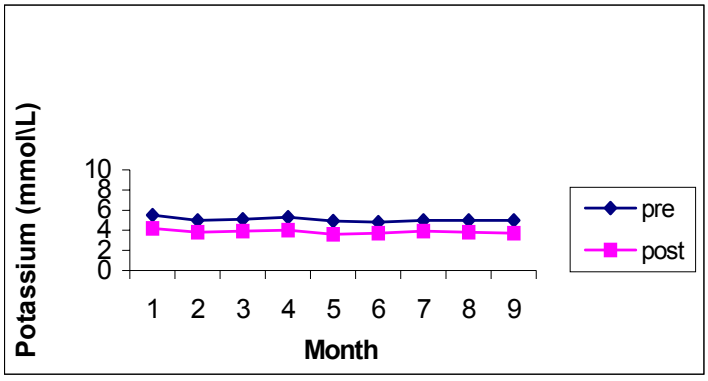

Figure 22: Pre and Post Haemodialysis Potassium Levels in the Intervention Group over Nine Months (p<0.001)

4.4.8 Comparison between pre and post potassium levels in the Control Group

In the control group the pre haemodialysis potassium levels ranged between 4.9 mmol/L and 5.2 mmol/L and were reduced to between 3.6 mmol/L and 3.8 mmol/L post haemodialysis. This reduction was statistically significant (p<0.001) at baseline (Figure 23).

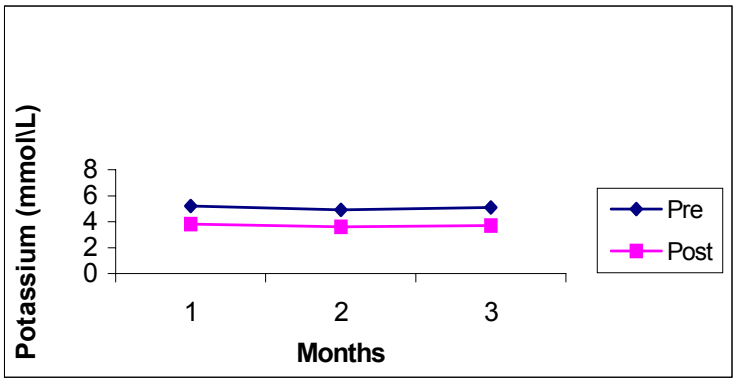

Figure 23: Pre and Post Haemodialysis Potassium Levels at Baseline in the Control Group (p<0.001)

From April to September the pre haemodialysis potassium levels ranged between 4.6 mmol/L and 5.1 mmol/L and were reduced to between 3.5 mmol/L and 3.8 mmol/L post haemodialysis. This reduction in post haemodialysis potassium levels were statistically significant ($p<0.001$). However, the potassium reduction at baseline was the same as the potassium reduction throughout the study.

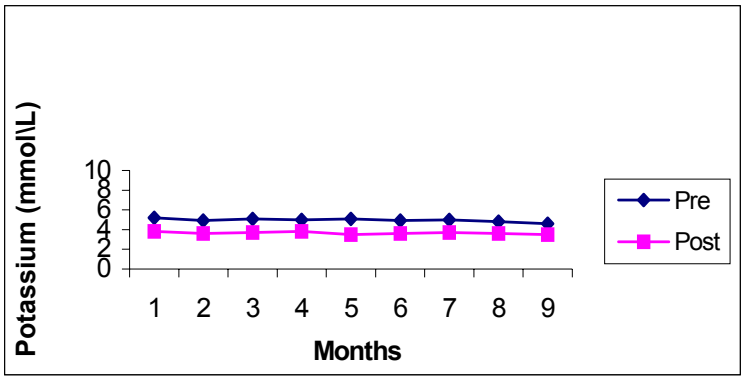

Figure 24: Pre and Post Haemodialysis Potassium Levels in the Control Group over Nine Months ($p<0.001$)

The potassium levels in the intervention group were reduced by 12% from January 4.2 ± 0.7 mmol/L to September 3.7 ± 0.5 mmol/L than the control group of 8% from January 3.8 ± 0.3 mmol/L to September 3.5 ± 0.2 mmol/L post haemodialysis. This suggests that there was a 4% greater difference in the reduction of potassium in the intervention group than the control group (Figure 24).

4.5 The Effect of Exercise during Haemodialysis on Oedema

Oedema of the lower limb was evaluated by measuring the diameter around the ankles both before and after haemodialysis. The difference in the diameter enabled us to determine whether exercise during haemodialysis caused a further reduction in oedema apart from the efficiency of the haemodialysis treatment. Oedema was confirmed when pitting of the ankles occurred when the ankle

circumference was greater than one centimetre. In some patients oedema was more visible in one ankle than the other, and in other patients oedema was visible in both ankles. In this study the right ankles and the left ankles were studied separately. The mean ankle circumference of the right ankle, over the study period, in the intervention and control groups is reflected in Table 7.

Table 7: Mean Right Ankle Circumference (cm) in the Intervention and Control Group

	Baseline			Intervention					
	Jan	**Feb**	**March**	**April**	**May**	**June**	**July**	**Aug**	**Sept**
Intervention Pre	25.8	26	26.2	26.6	26.5	26.2	26.3	25.7	25.7
Intervention Post	24.8	25	25.1	24.7	24.7	24.4	24.8	24.6	24.3
Control Pre	25.1	25.3	25.7	25.4	25	25.3	25	24.8	25.4
Control Post	24.5	24.5	24.8	24.6	24.3	24.5	24.4	24.4	24.5

4.5.1 Analysis of The Right Ankle In The Intervention Group

In the Intervention group the baseline values of the pre haemodialysis right ankle circumference remained constant showing no significant changes (p = 0.9). From April to September the pre haemodialyisis mean ankle circumference remained fairly constant with the values in April being 26.6 cm and September 25.7 cm showing no significant changes over the study period (p = 0.9. There was therefore no significant difference in the ankle circumference between April and September in comparison to the baseline period, pre haemodialysis (p = 0.5 (Figure 25).

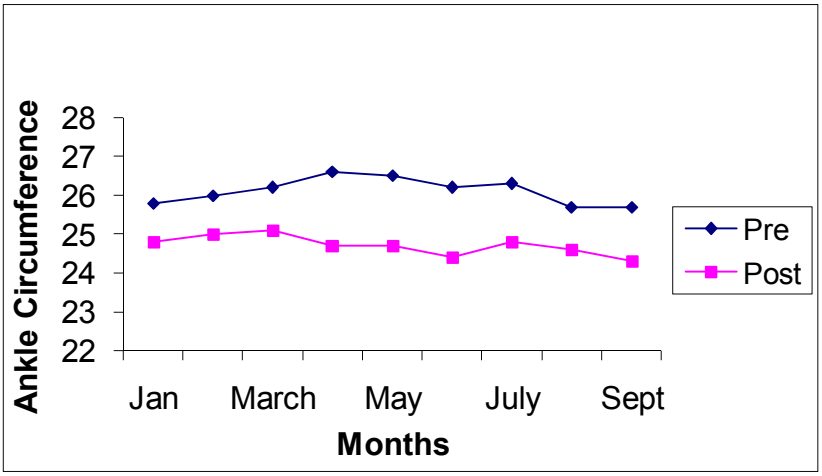

Figure 25: Mean Ankle Circumference of the Right Ankle in the Intervention Group over Nine Months (p=0.02)

The post haemodialysis mean ankle circumference at baseline showed no significant changes (p = 0.9. From April to September the mean ankle circumference remained constant with no significant changes (p = 0.9. However, the ankle circumference between April and September showed a significant difference in comparison to the baseline period because the values of the mean ankle circumferences between April and September were lower than the baseline period although remained constant. There was therefore a significant reduction in the right ankle circumference during the exercise period compared to the baseline period (p = 0.02 (Figure 25).

4.5.2 Analysis of the Right Ankle Circumference in the Control Group

The mean ankle circumference of the right ankle in the control group over the study period is reflected in Table 7. In the control group the pre haemodialysis baseline values remained constant, where the mean ankle circumference in January was 25.1 cm and 25.7 cm in March. There were therefore no significant changes at baseline pre haemodialysis (p = 0.9. From April to September the mean ankle circumference remained constant with the values in April and September 25.4 cm. This was therefore not significant (p = 0.9. There was

therefore no significant difference Pre haemodialysis in the right ankle circumference between baseline and April to September (p = 0.3). The post haemodialysis mean right ankle circumference at baseline remained constant with no significant changes (p = 0.9). From April to September the post haemodialysis ankle circumference showed no significant changes and remained constant (p = 0.9). There were therefore no significant changes in the mean ankle circumference of the right ankle in the control group at baseline in comparison to the period between April and September (p = 0.4) (Figure 26).

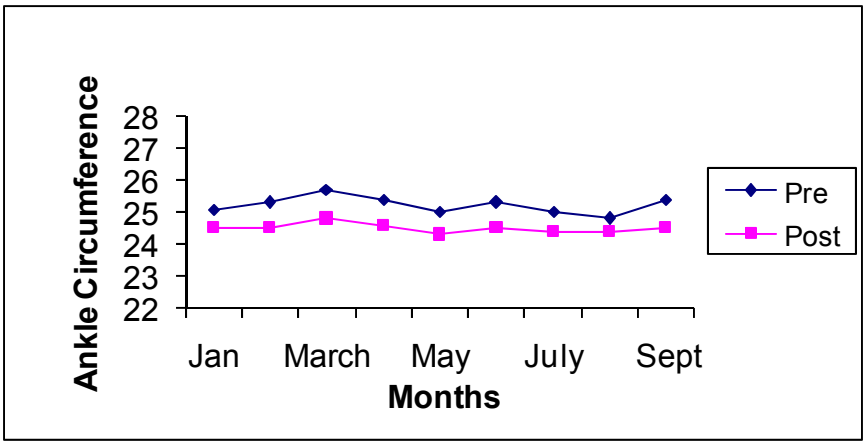

Figure 26: Mean Ankle Circumference of the Right Ankle in the Control Group over Nine Months

4.5.3 Pre and Post Haemodialysis Right Ankle Circumference in the Intervention and Control Groups

The change in size of the right ankle between pre and post haemodialyisis was calculated by subtracting the post haemodialysis ankle circumference from the pre haemodialysis. This is demonstrated in Table 8 and Figure 27.

Table 8: Changes in the Right Ankle Circumference (cm) between Pre and Post Haemodialysis in the Intervention and Control Group

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
Intervention	-1	-1	-1.1	-1.9	-1.8	-1.8	-1.6	-1.1	-1.4
Control	-0.6	-0.8	-0.9	-0.7	-0.6	-0.7	-0.6	-0.4	-0.9

The change between the pre and post ankle circumference of the right ankle at baseline showed no significant changes in the Intervention group (p = 0.3). From March to April there was a significant reduction in ankle circumference from –1.1 cm in March to –1.9 cm in April. In April, May and June the mean right ankle circumference remained constant at –1.9 cm, -1.8 cm and –1.8 cm, respectively. In July there was an increase in the right ankle circumference by – 0.2 cm and a further increase in August to –1.1 cm and a decrease again in September to –1.4 cm (Figure 27).

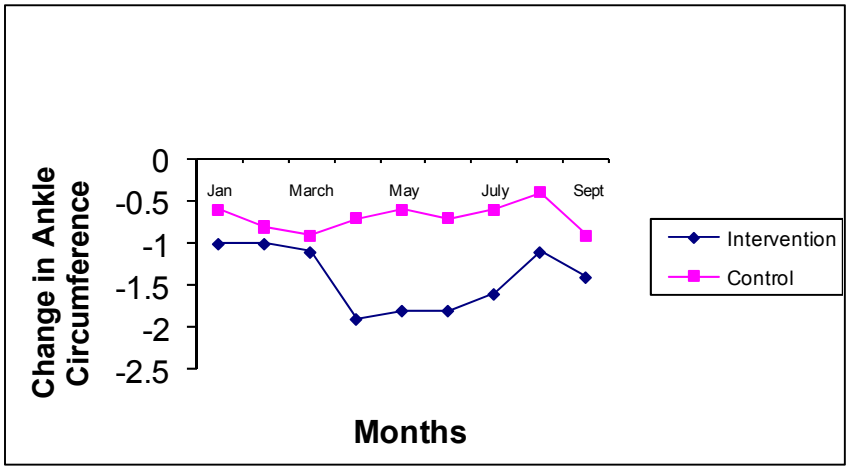

Figure 27: Changes in the Right Ankle Circumference between Pre and Post Haemodialysis in the Intervention and Control Group (p=0.004)

There was a significant reduction in the right ankle circumference in the Intervention group at the start of exercising in April and reduced four four-months and increased in the last three months of the study period. This increase in the

ankle circumference in the last three months showed no significant improvement in oedema (p = 0.6).

In the Control group the change in the ankle size between pre and post haemodialysis at baseline showed no significant changes (p = 0.7). From April to September the change in ankle circumference showed no significant changes (p = 0.3). The Intervention group showed a significant reduction in the right ankle circumference between April and September than the Control Group (p = 0.004).

4.5.4 Analysis of the Left Ankle Circumference in the Intervention Group

The mean left ankle circumference over the study period is reflected in Figure 28 and Table 9. In the Intervention group the pre haemodialysis ankle circumference at baseline showed no significant changes (p = 0.9). From April to September the pre haemodialysis ankle circumference showed no significant changes (p = 0.9), with the mean ankle circumference remaining between 26.2 cm and 26.9 cm and then dropped to 25.4 cm in September which had no effect over the overall study period. There was no significant difference in ankle circumference pre haemodialysis at baseline in comparison to the period from April and September (p = 0.5).

The post haemodialysis mean ankle circumference at baseline showed no significant changes (p = 0.9). The values remained at 25 cm and 25.1 cm at baseline. From April to September the mean ankle circumference post haemodialysis ranged between 24.1 cm and 24.8 cm which was fairly constant showing no significant changes (p = 0.9). However, from April to September the left ankle circumference values were lower than the baseline values which was significant (p = 0.002).

Table 9: The Mean Left Ankle Circumference (cm) in the Intervention and Control Groups

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
Intervention Pre	26.1	26.2	26	26.9	26.4	26.2	26.4	26.4	25.4
Intervention Post	25.1	25.1	25	24.6	24.7	24.6	24.6	24.8	24.1
Control Pre	25.2	25.4	25.5	25.3	24.7	25.1	24.8	25	25.7
Control Post	24.2	24.4	24.5	24.5	24.1	24.4	24.2	24.4	24.5

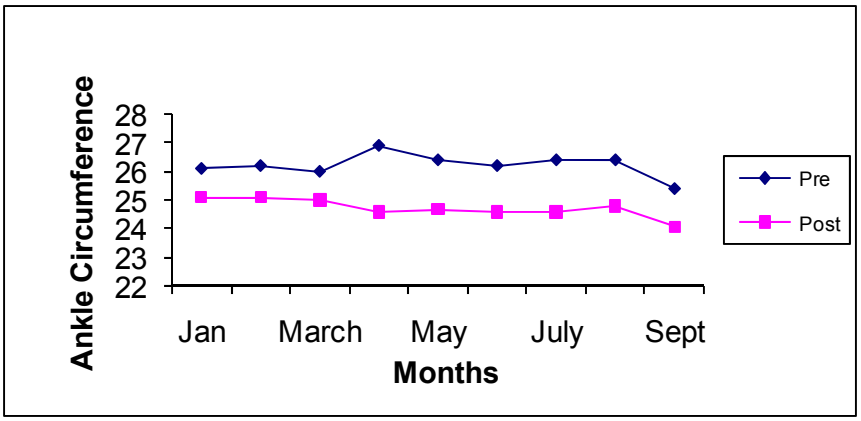

Figure 28: The Mean Left Ankle Circumference in the Intervention Group (p=0.002)

4.5.5 Analysis of the Left Ankle Circumference In the Control Group

The mean circumference of the left ankle in the control group over the study period is reflected in Table 10 and Figure 29. In the Control group the pre haemodialysis ankle circumference at baseline remained constant showing no significance (p = 0.9). The mean ankle circumference values at baseline remained between 25.2 cm and 25.5 cm.

Table 10: Changes in the Left Ankle Circumference (cm) Between Pre and Post Haemodialysis in the Intervention and Control Group

	Baseline			Intervention					
	Jan	Feb	March	April	May	June	July	Aug	Sept
Intervention	-1	-1.1	-1	-2.2	-1.8	-1.6	-1.9	-1.6	-1.2
Control	-1	1	-1	-0.8	-0.6	-0.8	-0.6	-0.6	-1.2

From April to September the mean ankle circumference was fairly constant showing no significant changes (p = 0.9. The values of the ankle circumference from April to September compared to the baseline, showed no significance (p = 0.2. The post haemodialysis ankle circumference at baseline showed no significant changes (p = 0.9). From April to September the left ankle circumference was fairly constant and flowed in a straight line in Figure 29. There was no significant changes in the left ankle circumference from April to September (p = 0.9). The values of the left ankle circumference between April and September in comparison to baseline were similar showing no significance (p = 0.7).

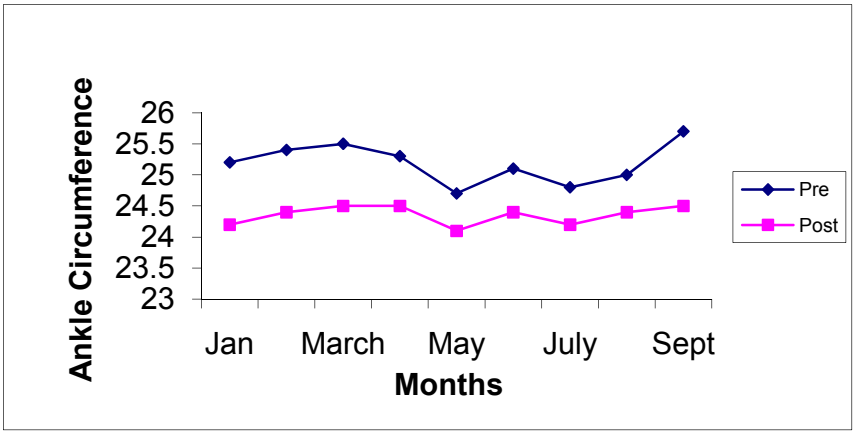

Figure 29: The Mean Left Ankle Circumference in the Control Group

4.5.6 Analysis of the Changes In the Left Ankle Circumference Between Pre And Post Haemodialysis In Both Groups

The change in size of the left ankle between pre and post haemodialysis was calculated by subtracting the post haemodialysis ankle circumference from the pre haemodialysis ankle circumference. This is reflected in Table 10 and Figure 30. The change between the pre and post ankle circumference of the left ankle at baseline showed no significant changes in the Intervention group (p = 0.9). From March to April there was a significant reduction in the ankle circumference were the ankle circumference in March was –1 cm and in April –2.2 cm. From April to May there was an increase in the ankle circumference from April –2.2 cm to May –1.8 cm. The ankle circumference remained constantly educed between May and August and the increased from –1.6 cm in August to –1.2 cm in September. The Intervention group in comparison to the Control group at baseline showed no significant changes in ankle circumference between the two groups (p = 0.8). There was a significant reduction in ankle size in the Intervention group than the Control group from April to September (p = 0.006).

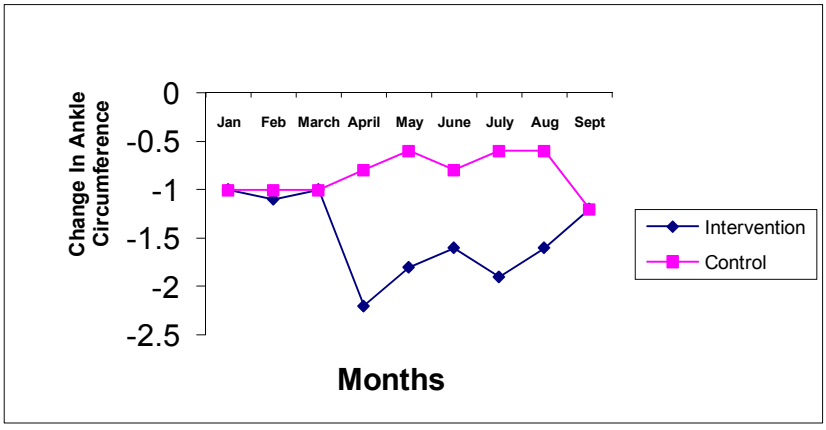

Figure 30: The changes in the Left Ankle Circumference between Pre and Post Haemodialysis in the Intervention and Control Group

In the control group the mean right ankle circumference at baseline and April to September in both pre and post haemodialysis showed no significant difference,

(p = 0.9). In the intervention group the mean right ankle circumference at baseline and April to September showed no significance in the pre and post haemodialysis (p = 0.9). The difference in the change of the right ankle size between the pre and post haemodialysis was calculated by subtracting the pre from the post haemodialysis ankle circumference. The difference in the change of the right ankle size in the control group at baseline and April to September showed no significance (p = 0.4). In the Intervention group there was a significant reduction in the difference of the ankle size by 45% between March and June (-1.1 cm in March to -1.9 cm in April, -1.8 cm May and -1.8 cm June) in comparison to baseline. From July to September the difference in the change of ankle size circumference in the intervention group increased and moved towards the baseline values, showing a 13% reduction in ankle circumference in comparison to baseline (p = 0.02).

The mean left ankle circumference in the control group and the intervention group both pre and post haemodialysis at baseline and April to September showed no significant differences. The left ankle circumference in the control group post haemodialysis at baseline and from March to September showed no significance in comparison to the pre haemodialysis left ankle circumference in the control group. In the control group the change in the ankle size between baseline and April to September showed no significance. In the intervention group the change in size of the left ankle from March to August showed a 60% decrease compared to baseline (p = 0.002). In August and September the change in the ankle size between pre and post haemodialysis ankle circumference increased from -1.6 cm in August to -1.2 cm in September, which was a 25% increase compared to baseline.

CHAPTER FIVE

DISCUSSION OF RESULTS

5.1 The Effect of Exercise during Haemodialysis on Urea

The serum urea levels in the intervention and control groups at baseline both pre and post haemodialysis showed no significant changes. From April to September the pre and post haemodialysis urea levels in the control group showed no significant changes. In the Intervention group the pre urea levels showed no significance but the post haemodialysis urea levels between April and September showed a significant reduction of 30%, $p<0.001$. This suggests that exercise during haemodialysis reduced the urea levels by 30% whereas there was no significant changes in the control group and the pre haemodialysis urea levels in the intervention group. The post haemodialysis urea levels in the intervention group at baseline compared to the pre haemodialysis urea levels showed a significant difference because the pre urea values, which were much higher at baseline (31.4 - 29.9 mmol/L) than the post urea levels (8.6 – 8.3 mmol/L). However, they both remained constant throughout the nine month period. The findings of this study were an overall 30% reduction in urea clearance in the Intervention Group, where the urea levels post haemodialysis in the intervention group was 5.0 ± 1.9 mmol/L compared to the control group, which was 8.9 ± 2.0 mmol/L. This was in contrast to the research done by Adorati (2000). Adorati (2000), had found that the total urea removal did not vary significantly with exercise (35.0 ± 10.5 g) compared to control (34.1 ± 12.1 g). The possible difference in the result of the two studies could be the sample size, where eight haemodialysis patients participated in Adorati's study, whereas fourteen patients participated in this study.

5.2 The Effect of Exercise during Haemodialysis on Creatinine

The creatinine levels in the control group pre and post haemodialysis at baseline, and April to September, showed no significant difference. The post haemodialysis creatinine levels showed a significant reduction at baseline and April to September. However, the reduction at baseline was the same throughout the study period. The creatinine at baseline and April to September pre haemodialysis ranged between 870 µmol/L - 970 µmol/L and 400 µmol/L - 450 µmol/L post haemodialysis. In the intervention group, the creatinine levels pre haemodialysis at baseline showed a significant reduction of 9%, P = 0.007. From April to June the creatinine levels were significantly reduced by 14% pre haemodialysis ($p<0.001$), and maintained consistency from July to September with no further reduction. The post haemodialysis creatinine levels at baseline showed a significant reduction of 17%, p = 0.01. The post haemodialysis creatinine levels from April to June showed a 19% reduction ($p<0.001$), and no significant changes in creatinine levels was observed from July to September. The post haemodialysis creatinine compared to the pre haemodialysis creatinine levels at baseline showed an 8% reduction. The post haemodialysis creatinine levels from April to June were reduced by 5% more than the pre haemodialysis creatinine levels and there was no significant difference in creatinine levels from July to September. In the intervention group the creatinine levels at baseline showed a significant reduction in comparison to the control group, p = 0.005. The intervention group showed a significant reduction in creatinine levels from April to September compared to the control group (P = 0.01). There was no significant difference between the two groups between July and September, p = 0.09. The intervention group, therefore, showed a greater reduction in creatinine levels at baseline and April to July than the control group. The possible reason for the patients in the intervention group having a larger reduction in creatinine levels pre haemodialysis and at baseline could be because patients were aware that this research project could improve the quality of their lives and possibly their

blood results. This motivated them to exercise on their non dialysis days, follow their renal diet more strictly and be more compliant with administering their medication promptly. This study is in agreement with the study by Adorati (2000), where the creatinine removal was significantly increased by exercise during haemodialysis (1852 ± 336 mg versus 1716 ± 288 mg), p = 0.005, in comparison to this study (441.7 ± 121.8 µmol/L versus 369.1 ± 107.6 µmol/L), p = 0.01. In another study done for a duration of eight weeks, exercise during dialysis enhanced dialysate urea removal but not serum urea clearance (Parsons, Toffelmire and King-VanVlack, 2004).

5.3 The Effect of Exercise during Haemodialysis on Potassium

The post haemodialysis potassium levels in both the intervention and control group showed an 8% reduction in potassium levels. This suggests that the potassium levels were not affected by exercise during haemodialysis. In the intervention group the post haemodialysis potassium levels in January was 4.2 ± 0.7 mmol/L compared to September which was 3.7 ± 0.5 mmol/L. This was a 12% reduction in potassium. In the control group the post haemodialysis potassium levels in January was 3.8 ± 0.3 mmol/L and September 3.5 ± 0.2 mmol/L. This was an 8% reduction. There was, therefore, a difference of 4% in reduction between the two groups over the study period, which was not significant. The potassium levels in this study dropped by 8% between April and September in both the intervention and control groups, both pre and post haemodialysis (p = 0.2) However, the potassium in the intervention group was reduced by 12% from January (4.2 ± 0.7 mmol/L) to September (3.7 ± 0.5 mmol/L) than the control group of 8% from January (3.8 ± 0.3 mmol/L) to September (3.5 ± 0.2 mmol/L) post haemodialysis. There was, therefore, a 4% greater difference in the reduction of potassium in the intervention group than the control group. This is in agreement with a previous study which proved that exercise during haemodialysis increases the efficiency of the dialysis treatment,

probably by reducing the rebound of solutes due to increased perfusion of the skeletal muscles (Dasselaar, Huisman and Franssen, 2004).

5.4 The Effect of Exercise during Haemodialysis on Kt/V urea

The Kt/V urea in the control group at baseline was 1.2 in January and February, and 1.3 in March, which was not significant ($p = 0.6$). There was an 8% increase in Kt/V urea from April to September ($P = 0.4$) and January to September, which therefore shows no significance. In the intervention group the Kt/V urea at baseline showed no significance, ($p = 0.2$), and the Kt/V values were 1.2 from January to March. From April to September the Kt/V urea increased by 8% ($p = 0.5$) and 17% from January to September ($p<0.001$). The intervention group showed an overall 9% increase in Kt/V urea than the control group between January and September. This study compares with the study published by Sun et al (2002). Their study showed that the Kt/V was higher in the intervention group than the control group, $p<0.05$. This study is also in agreement with the study by Parsons (2004) who demonstrated that the Kt/V increased 18% - 19% in the intervention group throughout the study period.

5.5 The Effect of Exercise during Haemodialysis on Oedema

The balance of sodium, through its dietary intake and renal excretion, determines extracellular fluid volume (ECV). Chronic renal failure and dialysis patients present with a positive sodium balance and increased ECV. Correction of ECV overload with ultrafiltration has led to the dry weight concept, which is the post dialysis body weight that allows BP to remain normal until the next dialysis session, without the need for antihypertensive medication despite interdialytic weight gain (Charra and Chazot, 2003).

The possible reason for the change in right ankle size in the intervention group between April and June (45%) could be because patients were interested in

being part of an investigation which could reduce the discomfort of ankle oedema and were motivated to do further exercising on their non dialysis days and complying strictly with their fluid restriction, diet and medication. From June to September the change in the difference on ankle circumference began increasing in the right ankle. The possible reason could be that patients were losing their excitement which they initially had to be part of a research project, and after feeling better they did not see a need to put in the same effort as they did between April and June because they felt well and reduced the extra lifestyle changes that they initially had.

The possible reason for the increase in left ankle size in the last month of haemodialysis could be because patients in the intervention group were not as enthusiastic as they were during the previous months because they were possibly feeling well and stronger from the previous months of exercising and did not feel that it was necessary to put in the same extra effort on their non dialysis days as they were previously doing because they felt well again.

CHAPTER SIX

CONCLUSION AND FUTURE WORK

The results of this study demonstrated benefits of exercise during haemodialysis on solute removal and oedema perhaps due to the acute increases in blood flow and therefore increasing perfusion of skeletal muscles. This study also showed a significant reduction in the solute levels and oedema. There was a significant 30% reduction in urea levels in the intervention group at the end of the nine month period. There was a 46% reduction in creatinine levels in the intervention group at the end of the nine month period. There was a 12% reduction in the potassium levels in the intervention group which was 4% more than the control group. The urea Kt/V in the intervention group showed a 9% greater reduction than the control group. There was a significant improvement in oedema of 45% of the right ankle for the first three months of exercise and thereafter there was an increase in ankle size in the last three months which was a 13% reduction in oedema compared to baseline. There was a significant improvement in oedema of 60% of the left ankle for the first five months of exercise and thereafter there was an increase in ankle size in the last month which showed a 25% reduction compared to baseline. The reason for the increase in ankle size in both ankles in the last three months is inconclusive and future investigation is recommended.

Therefore, exercise during haemodialysis is likely to prove an economic, safe and efficacious method for increasing the wellbeing of dialysis patients. However, future research is necessary to focus on the length and size of the study group to identify other beneficial effects of this intervention on solute removal and oedema and to identify the possible reasons for the urea Kt/V and creatinine levels remaining constant in the last three to four months and the increase in the change of ankle size in the last three months of the study period.

CHAPTER SEVEN

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