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Effects of resistance exercise training during hemodialysis on physical performance and health related quality of life

TESIS DOCTORAL

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Contents List

TABLES INDEX

FIGURES INDEX

PHOTOGRAPHIES INDEX

CHAPTER 1: INTRODUCTION

This chapter defines chronic renal failure stages until achieving End Stage Renal Disease. The different replacement therapies are reviewed, so as the health side effects that dialysis is not able to correct. Physical activity, physical function and survival of the cohort are reviewed. Finally, the literature on training modalities and its effects on patients' health are summarized. Gap in the literature and hypothesis are finally stated at the end of the chapter.

1.1. END-STAGE RENAL DISEASE AND RENAL REPLACEMENT THERAPIES.

Chronic renal failure (CRF) results from structural renal damage and diminished renal function, and may be caused by hypertension, diabetes mellitus, autoimmune reactions, infection, unknown cause, etc (1).

The kidneys' major functions include control of extracellular fluid volume, regulation of serum osmolarity, electrolyte and acid-base balances, secretion of hormones and excretion of uremic toxic substances (1-3). Kidney function is often measured by the Glomerular Filtration Rate (GFR), amount of filtration flux from blood to the Bowman's capsule generated at the glomerular capillaries of the nephrone (4). The normal rate is 90 ml/min/1,73m^2 and the stages of CRF are established according to the lost GFR, so that GFR between 60 and 89 ml/min/1,73m^2 corresponds to mild CRF, 30 to 59 ml/min/1,73m^2 corresponds to moderate CRF and less than 29 ml/min/1,73m^2 corresponds to severe CRF. End-stage renal disease (ESRD), in which there is

inadequate or nonexistent kidney function (1), occurs when GFR is bellow 15 ml/min/1,73m^2 (5).

When decreased GFR occurs the capacity of urine concentration of solutes is diminished, at first term poliuria occurs as a compensation mechanism and in last stages the kidney losses the capacity of urine excretion, so that fluid accumulation occurs (3). Sodium and potassium show a trend to increase in the last stages, what may be aggravated by diet intake, drugs, traumatisms, blood transfusions, etc. Metabolic acidosis due to the lack of capacity to excrete hydronium ions (H^+) occurs at the last stages, when bicarbonate decreases (3).

At the moment patient reaches a GFR bellow 5ml/min, frequently combined with plasmatic creatinine reaching 12-15 mg/dL and symptomatology of nausea, anorexia, asthenia and vomiting, one of the options of replacement therapy for renal function is needed. Conditions such as pericarditis, HTA, polineuropathy, diabetes and congestive heart failure accelerate the initiation of replacement therapy. The different replacement modalities are: dialysis techniques (hemodialysis, peritoneal dialysis, hemofiltration), that partially substitute kidney functions, or kidney transplantation that substitutes the whole functions of the kidney (3).

Hemodialysis (HD), the most common renal replacement therapy, is a process that replaces the excretory functions of the kidney through the use of a filter that contains a semipermeable membrane separating a rinsing solution from blood to filter out toxic waste substances from the blood. Additionally, HD allows for control of fluid and electrolyte balance (2,6). HD requires a vascular access, preferably long term, the most common being the arteriovenous fistula by anastomoses of radial artery and vein

at the forearm (2,6). In case of failure, graft may be required to get other accesses. The aim is to achieve a wide venous network with arterial blood, at a blood flux around 200 mL/min (6). Patients receive the treatment during 3 to 5 hours per session, 3 times per week, depending on residual renal function, body surface, HD technique and patient's disorders (2,6). The most common procedure to calculate the amount of HD per patient is by the calculation of Kt/V around 1.2, where K is urea clearance, t is length of HD session and V is patient's water volume (6). HD treatment is administered in hospital, in out-patient clinics or at home, after a training period and adaptation at home.

In Peritoneal Dialysis (PD), peritoneum acts as the semipermeable membrane that separates blood at the mesenteric capillaries and the periodically renewed fluid through an intraabdominal catheter. The total amount of solute excretion depends on the volume of liquid introduced per day at the peritoneal cavity, and compared to HD higher extraction of median molecules and lower extraction of small molecules is achieved. Patients requiring chronic PD follow most of the times a manual continuous technique (CAPD) that consists of introduction of 1.5 to 2.5 liters of dialysis solution four times per day. PD is specially recommended for patients suffering from ischemic cardiopathy, children and elderly, diabetics, and when troubles with vascular access are present (6).

Finally, renal transplantation from cadaver or form living donor is the most convenient replacement therapy for ESRD (6). If the intervention is successful, poliuria and normalization of nitrogen metabolism occurs and hydroelectrolitic reposition is required. Patients are at risk of acute or chronic rejection, infections due to inmunosupressor chronic treatment, cancer, arterial hypertension, cardiovascular complications, hyperparathyroidism, nephropathy of the transplanted kidney etc.

Survival of the transplanted kidney is about 90% at the first year, but decreases to 20% 20 years after the transplantation, and chronic nephropathy of the new kidney is the main cause for implant death (3).

The next section analyses how the uremic syndrome occurring at the ESRD by the impairment in renal function affects every other body system (2,3), and dialysis is not able to fully substitute the original kidney.

1.2. COMPLICATIONS OF KIDNEY FAILURE

1.2.1. CARDIOVASCULAR COMPLICATIONS

Cardiovascular complications are the main reasons for death in end-stage renal disease patients on HD, with mortality rates ranging from 30.4% in healthy HD patients to 56% in samples including diabetics older than 60 years (7-10). Left ventricular hypertrophy and coronary artery disease are reported in 30 to 70% of HD patients (11-13).

Cardiac morphological abnormalities described in HD patients (11) include higher size of right ventricle and left atrium, and higher left ventricular mass. Both the echocardiography at rest and the stress echo study show significantly greater end diastolic and systolic volume index, and lower ejection fraction (11) in HD patients compared to normal. While at rest patients achieve higher heart rate (11), at submaximal exercise heart rate is lower (11,14) and have lower increments of systolic blood pressure (14) compared to healthy subjects.

Risk factors capable of promoting the accelerated development of left ventricular hypertrophy and coronary atherosclerosis are prevalent in uremic patients receiving chronic maintenance HD (15-17). These include hypertension, arrhythmias, hemodinamic instability, pressure overload, anaemia, reduced levels of high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, commorbid diabetes mellitus and sedentary life-style.

Hypertension (HTA) is reported by 63 to 86% of HD patients (11,18,19), presenting higher values on systolic (16%) and diastolic (10%) pressure (11). It constitutes a major risk for cardiovascular morbidity and mortality in this cohort (20). Sustained activation of sympathetic nerve system mediates HTA in moderate and chronic renal insufficiency patients (20), and contributes to cardiovascular problems (left ventricular hypertrophy, arrhythmias) and kidney damage (21). The increased activity seems to be mediated by signals arising in the native kidneys that are independent of circulating uremia related toxins (22). HTA is associated with younger age, diabetes mellitus or HTA as cause of end-stage renal disease, less obese patients, fewer years in HD and higher number of medications (inadequate HTA control) (18).

Reduced heart rate variability (HRV) found in this cohort is associated with higher incidence of arrhythmias, clinical signs of uremic peripheral neuropathy (19) and sudden cardiac death in those HD patients who present signs of coronary artery disease (12). By the other hand, HRV index correlates with maximal oxygen consumption (19).

Other cardiovascular complications commonly found in ESRD patients are pericarditis, endocarditis, aortic valve stenosis and mitral valve calcification (17).

Therefore, a wide variety of cardiovascular risk factors commonly found in HD patients are eventually responsible for coronary artery disease and left ventricular hypertrophy that lead to death in a high percentage of ESRD patients.

1.2.2. MUSCULOSKELETAL ABNORMALITIES

Most of patients reaching ESRD are experiencing weakness, fatigue and lack of energy (23-29) which are considered the most important limiting factors for functional capacity (11,30). Decreased muscle strength and endurance on ESRD patients (28) are already present at the predialysis stage (26). Several morphological and metabolic alterations on the patient's skeletal muscle explain altered muscle function.

Both morphological and degenerative muscle abnormalities have been described in the literature. Morphological abnormalities include reduction in cross-sectional area (24,31), that predominantly affects anaerobic type IIb fibres (25,32-35), and that are not present earlier at predialysis stage (26). Nevertheless, in young CRF patients Wagner et al. (36) did not find those abnormalities. Degenerative changes reported in the uremic skeletal muscle include loss of myofilaments, and capillaries and mitochondrial changes, suggesting neuropathic atrophy (34,37,38), although Bradley et al. (33) findings did not support alterations in mitochondria's structure.

The uremic miopathy consists of muscle metabolism abnormalities that result in electromyographic changes and weakness (39). Two reviews highlighted the factors related with uraemic myopathy in patients with CRF (37,40). First, ESRD patients present central activation failure and decreased phosphorilation of creatine to creatine phosphate, as shown by Johansen et al. (23), despite previous studies did not

demonstrate abnormal creatine phosphokinase levels (32). Additionally, increased parathormone (PTH) as a result of decreased vitamin D leads to muscle weakness and fatigability by impairing energy production (32). Third, oxidative metabolism in the uremic muscle is altered (23). Oxygen transport from muscle capillaries into mitochondria is impaired (36,41). Uremic muscle presents fewer capillaries per fiber (36) and a significant decreased blood flow as a response to exercise (33) but not limited mitochondrial oxidative activity is found (36,41). Altered blood calcium levels may be responsible for capillary abnormalities that result in decreased skeletal muscle blood flow (37). Whereas, diminished oxygen transport contributes to the impaired oxidative metabolism that leads to exercise limitation in CRF patients.

In HD patients, muscle wasting occurs as a result of additional factors, both dialysis and non-dialysis-related, such as decreased dietary intake, impaired protein synthesis, sedentary lifestyle, and HD associated catabolism (25,42).

Summarizing, morphological (decreased type II cross-sectional area and degenerative changes) and metabolic abnormalities explain the impaired muscular function in ESRD patients.

1.2.3. HEMATOLOGICAL COMPLICATIONS

ESRD patients present 27% lower hematocrit compared with healthy subjects (37). Renal anaemia, which is normochromic and normocytic (17), is mainly due to decreased production of glycoprotein hormone erythropoietin (EPO) by endothelial cells in proximity of renal tubules that accompanies decreased GFR (43). Secondary factors contributing to anemia are faster destruction of red blood cells caused by uremic

environment and decreased erythropoiesis (3,43). It accounts for fatigue, dyspnea and increased cardiac output and left ventricular hypertrophy as a heart's compensatory mechanism for reduced oxygen delivery to tissues (17,43,44). Renal anemia emerges as an important factor affecting maximal exercise capacity in the patient with ESRD failure, and EPO administration increases maximal exercise capacity by increasing peak VO_2, showing positive central hemodynamic effects with reduction in left ventricular mass, volume and function (25).

Platelet quantity is usually normal in ESRD, but aggregation is impaired presenting disturbances at the level of endothelial contact (3,17,43), that may lead to bleeding at superficial sites such as skin and mucoses. Deep bleeding on muscles or joints does not occur because the coagulation system is not affected (17,43). The low hematocrit itself probably contributes to prolonged bleeding times (3,43).

Additionally deteriorated lymphocyte action is responsible for the decreased immunity found in this cohort (3), leading to higher risk of reactivation of tuberculosis and herpes zoster, a failure to clear hepatitis B, and a poor response to immunization with hepatitis B vaccines (17,45). Granulocites function in ESRD is also altered, so that the bacterizide action is impaired and infections incidence increase (3) mainly caused by violation of normal skin and mucosal barriers and not by immune system dysfunction (17,45).

1.2.4. NEUROLOGIC COMPLICATIONS

Uremia is accompanied by disordered functioning of both the central and peripheral nervous systems (3,17,46), and normalization occurs after restoration of normal biochemistry by transplantation (46). Neurologic problems arise in dialyzed patients as a complication of treatment, from metabolic derangements, or from disordered homeostasis (46).

Uremic encephalopathy may appear when GFR decreases to 10% of the normal value and typically leads to mental fatigue, confusion, impaired consciousness, difficulty concentrating, lethargy, myoclonic twitching of distal muscle groups and, pre-terminally, coma, all of them improving with dialysis (3,46). Other common abnormalities are the syndrome of neurologic dysfunction, which appears in the last part of HD and PD or shortly afterwards when uraemia is corrected rapidly, and chronic dementia in dialysis patients caused by aluminum poisoning or by progressive cerebrovascular disease from widespread atheromatous plaques that predispose patients to develop multi-infarct dementia (3,46). Brain swelling is believed to be the cause of restlessness, headache, nausea, vomiting and confusion.

Sleep disorder is a common complain of dialysis patients, and objective disorder in polysomnography is found in 50% of those patients (46). Most commonly seen alterations include insomnia, excessive daytime sleepiness, sleep apnea, periodic leg movements in sleep and restless legs (46).

Uremic neuropathy affects 70% of HD patients (11). It may manifests as a distal, symmetric, mixed motor and sensory polyneuropathy that typically involves the legs

more than the arms (3,17,46). This neuropathy presents as paresthesia in the feet, painful dysesthesia, ataxia and eventually weakness with foot drop, also loss of power in the small muscles of the hand, and is characterized by slowing of motor nerve conduction and sensory action potentials (3,46). A specific mononeuropathy of renal failure involves the median nerve at the wrist (carpal tunnel syndrome) (17,46), caused by β2-microglobulin-derived amyloid deposition (17). Autonomic neuropathy is responsible for abnormal responses in blood pressure and heart rate, so hypotension and tachycardia are commonly found during dialysis (11,17).

Despite renal failure can lead to many neurological problems, as detailed above, differential diagnosis for drug accumulation and vascular disorders is required before attributing problems to uraemia (17).

1.2.5. METABOLIC COMPLICATIONS

Several metabolic disturbances are associated with ESRD. First, carbohydrate metabolism is altered in renal failure due to glucose intolerance produced by resistance to insulin-mediated glucose uptake in skeletal muscle (3,17,47). Uremic skeletal muscle present reduced glycolisis and increased glucose muscle content (37,40) with glycogen deposition being more prominent in Type II fibres (34).

Second, there are complex effects on lipid metabolism, including reduction in catabolism of lipoproteins (3), which result in an increased concentration of very low-density lipoproteins (VLDL) and triglicerides, and a decrease in high-density lipoproteins (HDL) (3,15,44). ESRD patients present decreased carnitine content in uremic muscle (37,40), what results in impaired mitochondrial fatty acids oxidation and

in accumulation of acyl groups out of the mithocondria (48). Despite carnitine seems to affect skeletal muscle growth (25) and its deficiency negatively correlates with exercise performance (37,48), Rogerson et al. (49) could not demonstrate that L-carnitine supplementation results in improvement in muscle function or improvement in plasma lipid profile. The hyperlipidaemia of renal disease contributes to the high incidence of cardiovascular disease (15,44).

Finally, chronically uremic patients receiving any form of uremia therapy present lean tissue depletion and reduction of total body amount of albumin and other proteins (3,50,51). Factors contributing to net proteolysis in ESRD are metabolic acidosis (17,25,52), impaired protein synthesis, malnutrition and decreased energy intake (37,40,50).

1.2.6. HORMONAL COMPLICATIONS

Both intrarenal and extrarenal hormones are affected by ESRD (3,14,17,53). By one side, production of 1,25-dihydroxy vitamin D and erythropoietin is reduced (3,17,53), and by the other side, alterations on production, control, protein binding, catabolism, and tissue effect of extrarenal hormones in renal failure may be present (3,17,44). Hormone concentrations may be elevated as a result of reduced degradation (insulin, glucagon, cortisol, prolactine and growth hormone) (3,14,17,47,53), reduced renal excretion (norepinephrine and epinephrine) (53), or increased secretion in appropriate response to metabolic alterations (parathormone, plasma luteinising hormone, prolactine, growth hormone) (3,17,53). Hormone concentrations may be reduced owing to impaired production, as occurs with oestrogens and testosterone that lead to amenorrhea and impotence (3,17,53). Reductions in hormone-binding proteins

are most commonly a consequence of protein loss in nephrotic patients or in those on continuous ambulatory PD (17).

1.2.7. OSTEODISTROPHY

Renal bone disease, characterized by abnormal calcium/phosphate metabolism, is a result of the combination of secondary hyperparathyroidism (54), decreased metabolits of vitamine D and hyperphosphataemia (3,39,44). Failing of excretory function of the kidney when GFR declines leads to hyperphosphataemia, what has been directly associated to hyperparathyroidism (lost of calcium from bone), and indirectly due to inhibition of calcitriol (intermediate metabolit of vitamin D) (54). Other factors contributing to hyperparathyroidism are lack of calcitriol inhibition in parathyroid cells (54), lost of vitamin D metabolites bound to plasma-binding protein by urine, and to the tendency to hypocalcaemia (54,55). Calcitriol deficiency by decreased endocrine function of the kidney results in hypocalcaemia (44). Other factors contributing to hypocalcaemia are reduced calcium resorption in the intestine by insufficient active vitamine D (44,54), and partial resistance of the skeleton to PTH to release bone mineral and calcium. All these alterations are responsible for the appearance of osteitis fibrosa (increased bone turnover that results in rarefaction of trabeculae in bone) (54), osteomalacia (decreased mineralization of the bone matrix) (3,54), adynamic bone disease (decreased bone turnover that predisposes to hypercalcaemia) (54), osteopenia or osteoporosis. Pain (44), extra-osseus calcifications in the presence of local tissue lession (3,54) and fractures (56) are some of the consequences of bone disease in this cohort.

1.2.8. GASTROINTESTINAL COMPLICATIONS

A wide variety of gastrointestinal system disorders are commonly found in ESRD patients. Anorexia and nausea, associated with inadequate dialysis or hypotension (57), are commonly found in uraemic patients, both leading to decreased caloric intake and malnutrition (3,17). By the other side, many factors contribute to constipation found in ESRD patients, such as limitation on patients' fluid intake (17,57), decreased fiber intake due to potassium present in fruits an vegetables, calcium-containing phosphate binders and iron supplements intake, patient inactivity and narcotic analgesics. Constipation may predispose dialysis patients to diverticular disease (17,57). Patients suffering from diverticular disease, amyloidosis and constipation are more prone to present spontaneous colon perforation. Diarrhea may appear associated with dietary intake or viral disorder, as a consequience of prolonged antimicrobial therapy, due to infection (17,57). Hepatitis B, when contracted in the presence of renal failure is likely to become chronic due to the depression in cell-mediated immunity. Hepatitis C is common in renal units because of exposure to blood transfusions (17).

Other alterations affecting the gastrointestinal tract are metallic taste in the mouth, dyspepsia, angiodysplasia at submucosal and mucosal blood vessels, gastroparesis, isquemic bowel disease and bowel infarction, and acute pancreatitis (3,17,57).

1.2.9. OTHER ALTERATIONS: LUNGS, SKIN AND JOINTS

Pulmonary manifestations appear in ESRD patients because they are prone to develop pulmonary oedema with relatively small increases in extracellular fluid due to

increased capillary permeability in uremic syndrome. Pleuritis may appear combined with pericarditis (3,17) and pneumonia is an important cause of mortality in this population (58).

Concerning the skin, it presents a yellow-brown pigmentation in sun-exposed areas of ESRD patients, attributed to the retention of melanocyte-stimulating hormone, vegetable-derived lipochrome and carotenoids, and iron (3,17). Pruritus, an exasperating symptom associated with xerosis (dry skin) and warm skin, has a multifactioral origin that includes raised calcium phosphate product sensitivity to histamines, hyperparathyroidism, peripheral polyneuropathy and uraemia itself.

Finally, ESRD patients may present β_2-microglobulin amyloidosis, that results in arthropaty by deposits on large joints and spine, bone erosion, pathological fractures and tenosynovitis (3,17).

In summary, ESRD affects the whole body systems, and dialysis techniques are not able to fully normalize all of them. Survival of this cohort is not only affected by these body disturbances, but by other factors analysed in the following section.

1.3. FACTORS INFLUENCING SURVIVAL IN ESRD PATIENTS

Survival in HD patients has been found to correlate with factors of different nature.

The relationship between demographic and socioeconomic factors and survival has been analysed in the literature. Older age (7,10,59), male gender (10), smoking (10) and white race (59,60) have been associated with lower survival, although some studies did not support some of these findings (61,62). Variables that are not related with survival are educational level and marital status (61). Conversely, employment immediately before entering dialysis is associated with better survival (59).

Laboratory parameters and nutrition indicators also predict survival. Lower serum albumin level, as a sign of malnourished status, is associated with lower survival in HD (10,59,60,63) and in PD patients (64). While some studies found that low levels of other biochemical indicators of visceral and somatic protein content (serum albumin, prealbumin, creatinine and cholesterol), predicted mortality in maintenance HD patients (60), others did not find so (7,8,61). Liu et al. (8) clarified that, despite higher cholesterol is associated with higher mortality risk in the absence of inflammation in the general population, in HD patients lower cholesterol is associated with presence of inflammation, and thus the relationship between high cholesterol and better survival in HD patients is masked by inflammation. Friend at al (61) found that survival was related to higher blood urea nitrogen. The presence of chronic inflammation (brain natriuretic peptid and C-reactive protein) decreases survival (10). In predialysis patients, elevated serum levels of cellular adhesion molecules correlate with signs of inflammation, malnutrition and cardiovascular disease clinical signs, and are independent predictors of mortality once entering dialysis treatment (13). Several reviews highlight that low hematocrit level is associated to higher morbidity and mortality. According to Gómez y Carrera (65) proper hematocrit levels prevent from left ventricular hypertrophy, improve cognitive capacity, quality of life and physical functioning. Collins (66) concluded that low hematocrit of ESRD at entrance to HD

should be increased until levels ranging from 33 to 39%, unless patients present cardiac disease. In Elderly CKD patients risk of death after a myocardial infarction was higher if the hematocrit was low (67).

Diabetes, cardiovascular disease and longer time on HD treatment decreases survival (7,59,60,63,68). At predialysis stage, comorbidity is also associated with lower survival (13).

Hemodialysis adecuacy influences survival. Thus, Owen et al. (63) concluded, after analysing retrospectively 13.473 patients on HD, that urea reduction ratios during dialysis bellow 60% were associated with increased odds ratios for death. They found that diabetic patients had lower serum albumin concentrations and urea reduction ratios than non diabetic patients. According to Desmeules et al. (69) creatinine-based indices better predict survival than traditional urea kinetic models (KtV).

Physical activity (PA) level and physical functioning of HD patients predicts survival. Sedentary behaviour has been associated with increased risk of death at 1 year (59). Similarly, exercise capacity measured by VO_2 peak is a powerful predictor of survival over 3.5 years follow-up (7). Finally, higher handgrip strength increases probability of survival (64).

Health related quality of life (HRQoL) is defined as subject's subjective perception of level of wellbeing and satisfaction associated to life, and how it is affected by illness, accidents and treatments (77). HRQoL, as measured by the Medical Outcomes Survey short form (SF-36) subscales and components, has been analysed in relation to survival. By one hand, DeOreo (70) reported that physical function (PF)

scores were predictive of outcomes, so that patients scoring <34 on the physical component scale (PCS) had increased the probability to die or to be hospitalized. This measure predicted mortality so as catabolic rate or Kt/V. PF and general health, both subscales included in the PCS, have been associated with better survival (59). Additionally, the PCS in diabetic HD patients, and the mental component scale (MCS) in both diabetic and nondiabetic HD patients independently predicted mortality and morbidity in a Spanish study including 34 different hospitals (9). By the other side, attendance to group activities aimed to teach coping skills to HD and CRF through group discussions increase survival (61).

Concerning morbidity, Stehman-Breen et al. (56) found a higher risk of hip fracture on ESRD patients compared to general population, which was worsened in case of older age, female, Caucasian race, lower body mass index (BMI), and presence of peripheral vascular disease.

Therefore, survival is influenced by some modifiable factors, such as HRQoL, PA, and physical functioning, and interventions should address them in order to improve survival and decrease morbidity of ESRD patients in HD.

1.4. PSYCHOLOGICAL FEATURES OF PATIENTS ON HEMODIALYSIS

Evidence on three basic psychological features is found in this cohort: depression, anxiety and low HRQoL.

According to the literature, depression is found in 20 up to 66% of patients on HD (71-75), and it is a principal cause of fatigue upon arising (76). Concerning anxiety, rates on the literature range from 20 to 52% (71-73,75). Both depression and anxiety are associated with severity of symptoms such as vascular pain and restless legs (71).

HRQoL has been compared between general population and HD patients, and one of the most popular general tools to measure it is the Medical Outcomes Survey short form (SF-36), which gives measures of 8 subscales and two components, physical and mental. All subscales of SF-36 are significantly lower in HD patients compared to healthier counterparts (24,70,78-81), and this difference is more important in the physical function subscales (82). Factors such as diabetes (9), poor sleep (83), older age (84), female sex and diagnosis of musculoskeletal disease (81) are associated with lower HRQoL. Hemoglobin normalization so as nutritional status indicators (appetite, dietary energy intake, serum albumin and serum creatinine) have been found to be positively associated with HRQoL (85).

1.5. PHYSICAL ACTIVITY AND PHYSICAL FUNCTIONING IN HEMODIALYSIS PATIENTS

This section reviews the PA level in ESRD patients on HD and the factors influencing it. Physical functioning is defined, and evidence on HD patients is presented, measured with objective laboratory tests, functional performance tests and self-reporting measures.

PA is the movement of any part of the body produced by the contraction of the muscles that increases the energy expenditure (86). PA level has been found to be low

in HD patients, so that 60% are unable to perform any kind of activity apart from activities of daily living (ADL), 12,5% are unable to deambulate or transfer (59), and only 12% report the recommended levels of cardiovascular exercise (78). Additionally, only 6.6% of patients that are working at initiation of dialysis keep their job after 1 year (87).

PA measured directly by accelerometry in ESRD patients in HD is low compared to healthy counterparts (35% less active HD patients compared to sedentary healthy counterparts) (88). Indirect measure by PA questionnaires, as the seven-day recall questionnaire, showed lower activity levels is some studies (24,88,89) while in others (90) significant differences between PA in HD, CAPD and healthy controls were not found. It seems that activity questionnaires are designed for use in healthy populations and may be less sensitive to differences at the lower end of spectrum of activity (88).

Age is an important factor when looking at PA level of HD patient (59,88), so that PA declines in the dialysis patients at a rate of 3.4% per month over one year period (88). Other factors increasing the probability of low PA level are being woman, prevalence of cardiac disease and peripheral arterial disease, low predialysis systolic and diastolic blood pressure, HD treatment compared to PD, low educational level, and lack of employment before starting dialysis (59). A qualitative study identified mental and physical fatigue and low functional capacity as the main factors explaining the low PA level found in CRF patients (91). Creatinine and albumin concentration, as measures of nutritional status, correlate with PA level (92). Interventions giving specific information and encouragement to increase PA in HD patients result in increased activity level in this cohort (79).

Physical functioning is defined as an individual's ability to perform activities required in their daily living (93), and is determined by many factors, including physical fitness. Physical fitness is a set of attributes (cardiovascular fitness, strength and flexibility) that people have or achieve that relates to the ability to perform PA (86). Cardiorespiratory fitness is often referred to as exercise capacity, and it relates to the ability of the cardiac, circulatory, and respiratory systems to supply and use oxygen during sustained PA (86).

Physical Functioning can be measured using objective laboratory measures, physical performance testing or self-reported measures. It needs to be measured with different instruments to cover all areas, and tools should be tailored to specific population needs (94).

1.5.a. Objective laboratory measures

The graded exercise test (GXT) is a tool that objectively measures cardiorespiratory fitness, either measured by maximal oxygen uptake (VO_2 max), exercise time or METS (1 MET is the level of energy expenditure equal to 3,5 ml O_2/kg/min) achieved. Most ESRD patients stop this test due to muscular fatigue (11,34,85,95-97). In such cases the intensity achieved is not enough to stress the cardiorespiratory system and the test gives a measure of VO_2 peak (94). According to Sangkabutra et al. (98), a possible explanation of early muscle fatigue is the poor extrarrenal regulation of potassium during and following an incremental exercise test, although previous studies did not support this finding (96).

Exercise capacity has been found to be low in ESRD patients on HD. In their review Deligiannis et al. (11) concluded that reduction in peak VO_2 may achieve 50% of the general population values, with values around 15-25 ml/kg/min that are lower than other chronic diseases. Compared to renal transplant patients, HD patients present lower VO_2 peak values (95). Before EPO treatment was part of the patient's care routine, several studies showed a reduction on time (15,99-102) and VO_2 peak (14,15,47,99,100) attained on the GXT by young HD patients (29 to 38,5 years mean age, and Hemoglobin 7 to 8 g/dL), with mean values on HD patients showing a reduction of 44 to 50% compared to sedentary health controls.

Posterior studies with partial correction of anemia (39% lower hematocrit in HD group) by EPO, including samples of young HD patients (26 years old), showed reductions of 44% in VO_2 peak values compared to healthy sedentary controls (95,98). Studies where anemia correction achieved higher levels, reported as 27% lower hematocrit (11) or 15% lower hemoglobin (27,103,104), in HD patients (aged 44 to 63 years) still showed lower VO_2 peak values in HD patients that ranged from 61% to 19% (11,19,27,103-105). Several studies (85,106) compared patients with high (13 to 14g/dl) and low (10g/dl) hemoglobin levels and concluded that normalized hemoglobin level was associated with higher VO_2 peak both in young and old HD patients, although it remained below that predicted for comparable sedentary controls. The modest in VO_2 peak values after hemoglobin normalization could be explained by the significant reduction in peak blood flow to exercising muscle and remaining abnormally low values of O_2 conductance from muscle capillary to the mitochondria (107). This idea is supported by the fact that several studies report no improvement on exercise capacity after hemoglobin normalization (106,108). Painter et al. (106) found that increasing hematocrit using recombinant human EPO did not change VO_2 peak unless the patients

were involved in exercise training. Nevertheless exercise may not restore VO_2 peak normal values (11,27,30,105,106,109).

1.5.b. Physical performance testing

As highlighted by Painter (94), it is possible that more than 50% of dialysis patients are physically not capable of performing a symptom-limited exercise test. Rigor of progressive exercise testing as an outcome measure limits studies to only healthiest dialysis patients. Additionally, changes in VO_2 peak may not be sensitive measures of overall improvement in physical functioning as a result of interventions such as exercise training (110). The interest on physical functioning of older and diseased populations has lead to development of tests that measure physical performance of pre-determined tasks, such as walking during 6 minutes (6 minutes walking test, 6MWT), rising from a chair ('sit to stand' tests, STS 10 measuring time to perform 10 repetitions and STS 60 measuring repetitions performed on 60 seconds), stair climbing and gait speed. These tests are referred to as physical performance tests and are not direct measures of cardiovascular fitness, flexibility or strength but are indicators of physical fitness measures (94). Additionally, these tests referred by Mercer et al. (111) as functional capacity assessments may enhance information on the patient's nutritional status.

ESRD patients on HD present lower levels in physical performance tests compared to healthy sedentary counterparts (29,78,112-115) that are already evident on the predialysis stage (116). STS 10 in patients aged 43 to 60 years shows values that range from 50% (113,115) to 85% (78,117) bellow the sedentary population. Concerning 6MWT, values reported in the literature on patients of different ages (43 to 60 years old) range from 522 to 347 meters (29,78,114,115) which are bellow normal

values for sedentary healthy counterparts (118). General fatigue and weakness in the legs is reported by patients at tests termination (113).

Factors influencing performance tests are not only age and comorbidity, but also dialysis related factors such as Kt/V and albumin concentration (112,113). The relationship found between muscle cross sectional area, muscle strength and physical performance measures suggest that weakness from muscle atrophy is an important cause of reduced physical function (24).

1.5.c. Self-reported measures

Last possibility to measure physical functioning is by self-reported measures. Self-reported physical function can be assessed by the physical function (PF) subscale of the SF-36 (94), that measures to which extent the patient has limitation on daily PA. PF subscale deteriorates over time on the general population, and is lower in females than in males (119,120). Literature show lower PF in HD compared to healthy counterparts, with values that range from 11 to 47% (9,70,78,80,114,117,121,122) of those in healthy population. Physical scales deteriorate over time among HD patients (79).

Thus, PA level on HD patients is lower than sedentary healthy population. Physical functioning of ESRD population on HD is low when measured by objective laboratory measures, physical performance tests and/or self-reporting measures. In the next section a summary of the benefits achieved by HD patients exercising on different regimens are reviewed.

1.6. EVIDENCE ON EXERCISE BENEFITS FOR ESRD PATIENTS

During the last three decades different exercise programs have been implemented on CRF patients around the world. Tables I-III summarize, in three blocks (aerobic, progressive resistance training-PRT and combined exercise) the main characteristics and outcomes of the studies performed on this field of research. A whole overview highlighting the main facts of all the studies implementing exercise programs on HD patients is reported in Table IV.

1.6.1. AEROBIC TRAINING PROGRAMS

Concerning aerobic training (Table I) since 1980 until 2005, most of these studies (24/28) demonstrated a beneficial effect of exercise on the cardiorespiratory fitness (graded exercise test), while few of them evaluated the impact of the intervention on anxiety, depression and/or HRQoL (9/28). Additionally, very few of them included measures of physical functioning (7/28).

Table I. Aerobic Training Programs

Authors (year) Country	N	Study groups (age mean ± SD)	Exercise intervention			Outcomes		
			Delivery Design	prescription	weeks	Variable	%mean change	P
Eidemak et al. (1997) DENMARK (122)	30	Exercise N=15 (45) Control N=14 (45)	GFR= 25ml (min.1,73 m^2) RCT	Bycicle, swimming, running, walking 60-75% VO_{2max} 30 min Daily	72	VO_{2max} GFR Total cholesterol Triglycerides VLDL cholesterol LDL cholesterol HDL cholesterol	+8 -1,03 +13,22 -23,4 -4,17 +15,4 +4,9	0,05[b] NS 0,05[b] NS NS NS NS
Fitts et al. (1999) USA(123)	36	DC N=9 (48,7 ± 14,6) PC N=9 (50,1 ± 12,1) DR N=9 (44,7 ± 9,4) PR N=9 (44,4 ± 11,4)	HB RCT	RHB counselling Exercise couching Low I 14 strength-stretching exercises Independent walking Exercise diary 1h/week 1-3 months 1h/month 4-6 months	24	QoL (SIP) ↓ better DR PR Karnofsky DR ↓ worse PR Symptoms checklist DR PR 6MWT DR PR	↓ ↓ ↓ No ↑ ↓ -16,8 ↑ ↑	NS <0,05[a] - - NS <0,01[a] NS <0,01[b]
Goldberg et al. (1980) USA(99)	6	Exercise (37,3 ± 8,9)	ND	Cycle, walking, jogging, callisthenics 65-75% $VO_{2\ peak}$	36	Plasma triglyceride VLDL triglyceride HDL cholesterol Fasting plasma glucose glucose disappearance R Fasting plasma insulin Hematocrit Hemoglobin $VO_{2\ peak}$ GXT duration	+39,2 -44,3 +23,0 -6,3 +22,5 -40,1 +24,8 +29,0 +22 +41	<0,02 <0,02 <0,05 <0,01 <0,01 <0,01 <0,01 <0,04 <0,10 <0,02
Goldberg et al (1983)(100) Goldberg et al. (1986)(15) Harter et al. (1985)(124) USA	25	Exercise N=13 (40 ± 4) Control N=12 (36 ± 3)	ND RCT	Walking, cycle 50-80% $VO_{2\ peak}$ 45-60 min 3x/week	12	$VO_{2\ peak}$ GXT duration Plasma triglyceride VLDL triglyceride VLDL cholesterol HDL glucose disappearance R Insulin affinity Basal insulin levels Hematocrit RBC mass Hemoglobin RBC survival BDI (depression)	+17-21 +19-26 -23-33 -30-38 -16 +16-21 +35-48 +25-71 -20-21 +27 +27 +16-26 +46 -42	≤0,01[b] ≤0,01[b] ≤0,05[b] ≤0,05[b] ≤0,05[b] ≤0,02[b] ≤0,05[b] ≤0,01[b] ≤0,05[b] ≤0,01[b] ≤0,02[b] ≤0,01[b] ≤0,02[b] ≤0,01[b]
Konstantinidou et al. (2002) GREECE (30)	48	Exercise 1 N=16 (46,4 ± 13,9)	ND RCT	Aerobic training 60-70% HR_{max} 60 min 2x/week Swimm, basket, football 1x/week	24	Exercise group 1 VO_{2peak} GXT duration VE_{peak} VT	 +43 +33 +41 +37	 ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a]
		Exercise 2 N=10 (48,3 ± 12,1)	ID	Cycle 30 min ↓ I lower body strength and flexibility 30 min 70% HR_{max} 3x/week		Exercise group 2 VO_{2peak} GXT duration VE_{peak} VT	 +24 +22 +12 +18	 ≤0,05[c] ≤0,05[c] ≤0,05[c] ≤0,05[c]
		Exercise 3 N=10 (51,4 ± 12,5) Control N=12 (50,2)	HB	Home program Cycle and flexibility 50-60% HR_{max} 5x/week		Exercise group 3 VO_{2peak} GXT duration VE_{peak} VT	 +17 +14 ↑ +8	 ≤0,05[c] ≤0,05[c] ≤0,05[c] ≤0,05
Koufaki et al. (2002a)(90) UK	33	Exercise N=18 (57,3) Control N=15 (50,5) HD+PD	ID RCT	Cycle 90% VT 2 bouts x 20 minutes 3x/week	12	VO_{2peak} VO_2-VT GXT workload Oxygen Uptake kinetics STS 5 STS 60 NSRI walk	+15,8 +11,7 +27,4 -25,79 -22,3 +29 ↓	<0,05[a] <0,05[a] <0,05[a] 0,059 <0,05[a] <0,05[a] -
Koufaki et al (2002b)(92) UK	18	Exercise 8 HD+10 PD (54,3 ± 17,1)	ID	Cycle 90% VT 40 minutes 3x/week	24	VO_{2peak} % patients ↑ >SEM 3 m % patients ↑ >SEM 6 m VO_2 kinetics % patients ↑ >SEM 3 m % patients ↑ >SEM 6 m	+9,6 61 89 +23,8 55 55	<0,05 - - <0,05 - -

Authors (year) Country	n	Study groups (age mean ± SD)	Exercise intervention			Outcomes		
			Delivery Design	prescription	weeks	Variable	%mean change	P
Kouidi et al. (1997)(71) GREECE	31	Exercise N=20 (49,6 ± 12,1) Control N=11 (52,8 ± 10,2)	ND RCT	Cycle, walking/JOG, callisthenics, aerobics, swimming, ball games 50-70% VO_{2peak} 90 min 3-4x/week	24	VO_{2peak} GXT duration BDI (depression) QLI – patient activity QLI – daily living QLI – health QLI – support QLI – outlook	+38,1 +40,8 -34,8 ↑ ↑ ↑ ↑ ↑	≤0,05[b] ≤0,05[b] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a]
Kouidi et al. (2004)(125) GREECE	34	Exercise 1 N=16 (52,9 ± 11,3)	ND RCT	Aerobic training 60-80% HR_{max} 60 min 2x/week Swimm, basket, football 1x/week	4 years	After 1 year Exercise 1/ Exercise 2 VO_{2peak} GXT duration VE_{peak} VT HR_{peak}	 +47+34 +38+26 +24+13 +39+29 ↑	 ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05
		Exercise 2 N=18 (53,5 ± 10,8)	ID	Cycle and coordination + ↓ I lower body strength exercise RPE 13 60-90 min 3x/week		After 4 year Exercise 1/ Exercise 2 VO_{2peak} GXT duration VE_{peak} VT HR_{peak}	 +70+50 +53+43 +43+26 +52+42 ↑	 ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05
Levenglou et al. (2004)(126) TURKEY	14	Exercise (33,1 ± 13,1)	ND	10 min warming-up 60 min cycling 10 min stretching 10 min cool-down I 40-60% peak HR 3x/week	12	VO_{2peak} GXT duration GXT workload STS 10 6MWT BDI (depression) KDQoL SF-36 PCS KDQoL SF-36 MCS	+20 +27 +20,8 -16,9 +18,8 +28,6 - -	0,006 0,002 0,002 <0,001 0,002 <0,001 0,002 0,004
Macdonald et al. (2005)(127) UK	9	Exercise (48,4 ± 5,3)	ID	High I cycle RPE 9 warming-up RPE 17 main phase RPE 7 recovery 2 min x 15 times 3x/week	12	LBM Quadriceps strength STS 30 IGF-I, IGFBP-3 BP medications	No ↑ +19 +20 No ↑ -30	- <0,05 <0,05 - <0,05
Miller et al. (2002)(128) USA	56	Exercise N=24 (52,8 ± 16,0) Control N=32 (56,1 ± 15,2)	ID No RCT	Cycle to tolerance ≤30 min 3x/week	24	BP Number of anti-HP Expenditure on anti-HP	No ↓ -36% ↓	- 0,018[a] 0,005[a]
Molsted et al (2004)(82) DENMARK	20	Exercise N=11 (59) Control N=9 (48)	ND RCT	Step exercise, cycle, aerobics RPE 14-17 60 min, 2x/week	20	VO_{2peak} SF-36 P Functioning SF-36 Bodily Pain SF-36 PCS	↑ ↑ ↑ ↑	0,012[a] 0,01[a] 0,03[b] 0,004[b]
Moore et al. (1993)(31) USA	11	Exercise (47,3)	ID	Cycle ≥ 70% HR_{peak} RPE 6/10 ≤60 min 3x/week	12	VO_{2peak} Peak workload Submaximal HR PFK activity Type I muscle fibre area type II muscle fibre area Capillaries/fibre Ratio	+13,5 +16,6 ↓ ↑ No ↑ No ↑ No ↑	<0,1 ≤0,05 ≤0,05 ≤0,05 - - -
Moros et al. (1995)(129) SPAIN	10	Exercise N=6 (67) Control N=4 (66)	ND RCT	Aerobic exercise	18	Systolic BP_{peak} Diastolic BP_{peak} HR_{max} GXT duration GXT workload FVC GHQ (↑ improvement) Hematocrit	-0,9 -11,6 +1,1 +18,2 30,7 ↑ ↑ +14,2	NS NS <0,05[b] <0,05[b] <0,05[b] <0,05[b] - <0,05[b]
Moros García et al. (2000)(105) SPAIN	34	Exercise N=23 (40 ± 16) Control N=11 (32 ± 12)	ND RCT	10 min warming-up 30 min cycling 15 min games I 50-70% HR_{peak} 3x/week	18	Systolic BP_{rest} Diastolic BP_{rest} VO_{2peak} VCO_2 GXT duration GXT workload HR_{max} Systolic BP_{max} Diastolic BP_{max}	-8,5 -5,5 +24,4 +27,8 +29,1 +36,2 +3,7 -3,4 -5,7	<0,01[b] <0,01[b] <0,001[b] <0,001[b] <0,001[b] <0,001[b] NS NS NS

Authors (year) Country	n	Study groups (age mean ± SD)	Exercise intervention			Outcomes		
			Delivery Design	prescription	weeks	Variable	%mean change	P
Mustata et al (2004)(130) CANADA	11	Exercise (55,5 ± 4)	ND	Treadmill or cycle 60 min 2x/week	12	Arterial stiffness Pulse pressure (mm Hg) Systolic BP Insulin resistance	↓ ↓ ↓ No ↑	0,01 <0,05 <0,05 -
Painter et al. (1986)(101) USA	20	Exercise N=14 (42 ± 10) Control N=6 (42 ± 16)	ID No RCT	Cycle 65-85% VO_{2peak} 30-45 min 3x/week	24	VO_{2peak} at 3rd month VO_{2peak} at 6th month Vertical work capacity Hematocrit Total cholesterol HDL-cholesterol	+17 +23 +40 No ↑ No ↓ No ↑	≤0,05[b] ≤0,05[b] ≤0,05[b] - - -
Painter et al. (2002)(106) USA	48	Exerc.+EPO N=12 (43,5) Exercise N=10 (47,6) EPO only N=12 (50,1) Control N=14 (43,3)	ID RCT	Cycle RPE 12-14 70% HR_{peak} Intervals 2-3min RPE 15-17 30 min 3x/week	20	Post-hoc analysis exercise groups: VO_{2peak} SF-36 Physical Function	 9,6-15,7 ↑	 0,028[a] 0,015[a]
Parsons et al. (2004)(131) CANADA	13	Exercise N=6 (60) Control N=7 (49)	ID RCT	Cycle 40-50% maximal work capacity 45 min (15 min/hour) 3x/week	8	GXT workload Blood urea clearance Dialysate urea clearance QoL (SF-36)	No ↑ No ↑ ↑ No ↑	- - ≤0,05[b] -
Pechter et al. (2003)(132) ESTONIA	26	Exercise N=17 (52) Control N=9 (48)	Moderate CRF No RCT	↓ I aerobic exercise vertically in pool 24ºC Shoulder immersion 10 min warming-up 10 min 10 min cool-down 2x/week	12	VO_{2peak} GXT workload Systolic BP_{rest} Diastolic BP_{rest} Cystatin-C in serum GFR LPO GSH	+2,1 +14,9 -5,4 -3,4 -17,6 +6,7 -34,4 +15	NS <0,05[b] <0,05[b] <0,05[b] <0,05[b] NS <0,05[b] <0,05[b]
Sakkas et al. (2003)(35) UK	15	Exercise 6 HD + 9 PD (60 ± 12)	ID	Cycle 90% VT 40 min continuous 3x/week	24	CSA gastrocnemius Type I fibres Type II_a fibres Type II_X fibres Atrophy % Type I Atrophy % Type II_a Atrophy % Type II_X Capillary profile	46 32 54 36 -36 -37 -30 +24	<0,01 <0,01 <0,01 NS <0,05 <0,05 <0,05 <0,05
Shalom et al. (1984)(102) USA	14	Exercise N=14 Compliant (46,4); Non compliant (44,4)	ND	Cycle, walking, jogging, callisthenics Up to 75-80% HR_{max} 45 min, 5 x/week	12	GXT workload VO_{2peak} (compliant) Oxygen pulse (compliant) STAI (anxiety,↑ worse)	↑ ↑ ↑ No ↓	<0,05 0,001 0,026 -
Storer et al. (2005)(27) USA	24	Exercise N=12 (44 ± 9) Control N=12 (39 ± 9) Healthy N=12 (44 ± 12)	ID No RCT	Cycle 50% Peak work 20 min at initiation until 40 min 3x/week	9	VO_{2peak} Endurance time GXT workload Strength 5 RM leg press Power (watts/Kg) Fatigability Stair climbing task Timed up-and-go Walking speed	+22 +144 +46 +16 +15 +43 +14 +12 +19	<0,05[a] <0,05[a] <0,05[a] 0,002[a] <0,05[a] <0,05[a] 0,031[b] 0,012[b] 0,003[b]
Suh et al. (2002)(133) KOREA	14	Exercise (42 ± 10)	ND	Bicycle ergometer, treadmill, upper limb ergometer 60 min 3x/week	12	Hematocrit VO_{2peak} GXT duration STAI (anxiety ,↑ worse) Depression (↑ worse) QoL	+1,43 +13,3 +25,6 -10,6 -11,4 +7,3	NS 0,013 0,002 0,004 0,073 0,031
Violan et al. (2002)(95) SPAIN	21	Exercise N=9 HD (27,1 ± 4,1) N=12 TX (35,1 ± 12,9)	ND	Stretching, walking, jogging, ball games 60% peak HR 50 min 3x/week	24	VO_{2peak} HR_{max} Minute ventilation GXT workload VT	+7,7 No ↑ No ↑ No ↑ No ↑	NS - - - -

Anti-HT = Anti-hypertensive medications; **BDI** = Beck Depression Inventory; **BP** = Blood Pressure; **CRF** = Chronic Renal Failure; **CSA** = Cross Sectional Area; **DC** = Dialysis control; **DR** = Dialysis rehabilitation; **EPO** = Erythropoietin; **FVC** = Forced Vital Capacity; **GFR** = Glomerular Filtration Rate; **GHQ** = General Health Questionnaire; **GSH** = Glutathione reduced form; **GXT** = Graded Exercise Test; **HB** = Home Based; **HD** = Hemodialysis; **HDL** = High Density Lipoprotein; **HP** = High Pressure; $\mathbf{HR_{max}}$ = Maximal Heart Rate; **I** = Intensity; **ID** = Intra-dialysis; **IGF** = Insulin-like Growth Factor; **IGFBP-3** = IGF binding protein 3; **JOG** = Jogging; **LBM** = Lean Body Mass; **LPO** = Products of lipid peroxidation; **m** = Months; **min** = Minutes; **MCS** = Mental Component Scale; **ND** = Non-dialysis time; **No RCT** = Nonrandomized Controlled Trial; **NS** = Non significant; **NSRI walk** = North Staffordshire Royal Infirmary walk Test; **P** = Physical; **PC** = Predialysis control; **PCS** = Physical Component Scale; **PD** = Peritoneal Dialysis; **PFK** = Phosphofructokinase; **PR** = Predialysis rehabilitation; **QLI** = Quality of Life Index; **QoL** = Quality of Life ; **R** = Rate; **RBC** = Red Blood Cell; **RCT** = Randomized Controlled Trial; **RHB** = Rehabilitation; **RPE** = Rate of Perceived Exertion; **SEM** = Standard Error of Measurement; **SF-36** = Medical Outcomes Survey Short Form; **SIP** = Sickness Impact Profile; **STAI** = State Anxiety Inventory; **STS** = Sit to Stand to Sit test; **TX** = Renal Transplant; $\mathbf{VE_{peak}}$ = Peak Ventilation; $\mathbf{VO_{2\ max}}$ = Maximal Oxygen Consumption; **VLDL** = Very Low Density Lipoprotein; **VT** = Ventilatory anaerobic Threshold; ↓ = Decrease; ↑ = Increase; **6MWT** = Six Minutes Walking Test

[a] Significant change over time vs. comparison group.

[b] Significant vs. baseline values within group.

[c] Significant vs. control group only.

1.6.2. PROGRESSIVE RESISTANCE TRAINING PROGRAMS

All the PRT studies (Table II) were implemented more recently (since 2001 until 2008) and demonstrated an increase in strength (8/9), and only some of the studies reporting results on physical functioning tests demonstrated an improvement (4/6). Similarly, improvement on HRQoL was found in 3 out of 4 studies.

Table II. Progressive Resistance Training Programs

Authors (year) Country	N	Study groups (age mean ± SD)	Exercise intervention			Outcomes		
			Delivery Design	prescription	weeks	Variable	%mean change	P
Castaneda et al. (2001)(134) Castaneda et al. (2004)(135) USA	26	PRT + ↓ protein diet N=14 (65 ± 9) Placebo EX + ↓ protein diet N=12 (64 ± 13)	GFR ≈ 25ml (min.1,73 m^2) RCT	Placebo: stretching and flexibility EX PRT: UL and LL: chest press, latissimus pull-down, knee flex-ext, leg press 80% 1RM 3 sets x 8 reps 45 min. 3x/week	12	Strength Total potassium Type I fibre area Type II fibre quadriceps C- reactive protein Interleukin-6 Albumin Transferrin Weight	+32 +4 +24 +22 -21,8 -37,2 +3 +44,9 ↑	<0,001[b] 0,014[b] 0,031[b] 0,045[b] 0,049[b] 0,012[b] NS 0,042[b] 0,049[b]
Cheema et al (2007)(114) Australia	49	Exercise N=24 (60 ± 15,3) Control N=25 (65 ± 12,9)	ID RCT	10 exercises (shoulder press, side raise & ER, triceps ext, biceps curl; knee ext & flex, hip flex & abd, SLR) 2 sets x 8 reps RPE 15-17 3x/week	12	Muscle CSA Total Strength BMI SF 36 Physical Function SF 36 Vitality 6MWT	+1,15 +15,5 +1,11 +10,3 +4,8 +3,4	NS 0,002[a] 0,02[a] 0,02a 0,02[a] NS
Headley et al (2002)(115) Nindl et al (2004)(136) USA	10	Exercise (42,8 ± 4,4) HD vintage (41,6 ±19 months)	ND HB	Machine weight exercises (9) UL, LL 3 sets x 15 reps RPE<15 2x/week Exercises with elastic bands at home 1x/week	12	Peak torque at 90º 6MWT Maximal walking speed STS-10 Percentage body fat C-reactive protein Total IGF-I IGF-1:IGFBP-3 x 10 Ratio	+12,1 +4,7 +7,1 -12,31 +7,1 -50,7 -15,4 -21	≤0,05 ≤0,05 ≤0,05 ≤0,05 ≤0,05 - ≤0,039 ≤0,003
Heiwe et al. (2001)(116) SWEDEN	25	Exercise N=16 (76±7) Control N=9 (72±6)	GFR≤ 25ml (min.1,73 m^2) No RCT	Knee ext 3 sets x 20 reps 60% 1RM 60 movements per min Static endurance 5 sets x 1 rep (5 sec) 30 min group EX 3x/week	12	Strength (1RM) Static endurance Dynamic endurance 6MWT Test 'up and go' QoL (SIP)	+62,5 +14,3 +29,7 +15,9 -18,2 No ↑	0,0001 NS 0,004 0,002 0,004 -
Heiwe et al. (2005)(26) SWEDEN	12	Exercise N=7 (76±8) Control N=5 (71± 5)	GFR≤ 25ml (min.1,73 m^2) No RCT	Knee ext 3 sets x 20 reps 60% 1RM 60 movements/ min Static endurance 5 sets x 1 rep (5 sec) 30 min group EX 3x/week	12	Strength Dynamic muscular endurance Type I fibre area Type IIA fibre area Type IIB fibre area	+40 +48,6 ↑ ↑ No ↑	0,006 NS NS NS NS
Johansen et al. (2006) (121) USA	79	Exercise N=20 (54,4 ± 13,6) Nandrolone+ Exercise N=20 (55,5 ± 12,5)	ID RCT	Knee extension Hip flex, abduction Ankle dorsiflex, plantar flex Ankle weights 60% 3RM 3sets x 10 reps 3x/week	12	LBM Quadriceps CSA Strength Physical Activity (Accelerometry) STS 5 SF 36 Physical Function	-0,63 +2,5 +61,4 +28,4 -16,1 +23	NS 0,02[a] <0,0001[a] NS NS 0,03[a]
		Nandrolone N=19 (55,7 ± 13,4) Placebo N=20 (56,8 ± 13,8)	ID	Weekly nandrolone decanoate (100 mg ♀;200 mg ♂) or placebo intramuscular injection		LBM Quadriceps CSA Strength Physical Activity STS 5 SF 36 Physical Function	+7,2 +9 +10,7 +65,8 -12,2 +6,5	<0,001[a] <0,001[a] NS NS NS NS
Segura et al. (2008)(137) SPAIN	16	Exercise N=8 (54,9 ± 15,6) Control N=8 (68,8 ± 16,2)	No RCT	10 min stretching and 25 min 4 Ex (knee Ext, triple extension ism and elastic band, double knee ext ism) 3sets x 15 reps RPE 12-15 3x/week	24	GXT workload (METS) GXT duration (N=7) 6MWT (N=7) STS 10 (N=7) STS 60 (N=7) SF-36 PCS SF-36 MCS	+12,6 +15,9 +18 -21,4 +9,9 -8,4 +21,2	0,17[c] 0,23[c] 0,009[c] 0,013[c] 0,04[c] - 0,05[c]

Abd = Abduction; **CSA** = Cross Sectional Area; **ctrol** = Control; **BMI** = Body Mass Index; **ER** = External Rotation; **EX** = Exercise; **Ext** = Extension; **Flex** = Flexion; **GFR** = Glomerular Filtration Rate; **HB** = Home Based; **HD** = Hemodialysis; **ID** = Intra-dialysis; **IGF** = Insulin-like Growth Factor; **IGFBP-3** = IGF binding protein 3; **LBM** = Lean Body Mass; **LL** = Lower Limbs; **min** = Minutes; **ND** = Non-dialysis time; **No RCT** = Nonrandomized Controlled Trial; **NS** = Nons significant; **PRT** = Progressive Resistance Training; **QoL** = Quality of Life ; **RCT** = Randomized Controlled Trial; **reps** = Repetitions; **RM** = Resistance Maximum; **RPE** = Rate of Perceived Exertion; **sec** = Seconds; **SF-36** = Medical Outcomes Survey Short Form; **SIP** = Sickness Impact Profile; **SLR** = Straight Leg Raising; **STS** = Sit to Stand to Sit test; **UL** = Upper Limbs; ↑ = Increase; **6MWT** = Six Minutes Walking Test

[a] Significant interaction between time and the intervention. [b] Significant change over time vs. comparison group.

[c] Significant vs. baseline values within group.

1.6.3. COMBINED TRAINING PROGRAMS

Finally, Table III summarizes the main facts of 12 studies reviewed on combined (aerobic plus some PRT) exercise programs, which were implemented since 1991 until 2005. Most of the studies (5/6) evaluating the effect of the program on the cardiorespiratory fitness (graded exercise test) demonstrated a beneficial effect. Strength improved in all the studies that measured this variable (4/4), while the intervention improved physical functioning tests in 4 out of 5 studies. Additionally, 5 studies evaluated the impact on HRQoL measured by different questionnaires. From them, the study with the highest sample size of all studies reviewed (79) found positive effect of the intervention in four out of eight subescales of the SF-36 and in the PCS, but no effect was found on the MCS.

Table III. Combined Training Programs

Authors (year) Country	N	Study groups (age mean ± SD)	Exercise intervention			Outcomes		
			Delivery Design	prescription	weeks	Variable	%mean change	P
Cappy et al. (1999)(138) USA	16	Exercise (53,9 ± 15) Years on HD 4,9 ± 5,6	ID	Cycle, treadmill 30 min Stretching and Light weight strengthening exercise	12	STS-60 60 second stair climb 60 second leg lifts Slow walk 8,5m Brisk walk 8,5m Blood phosphorus Pre-HD SBP	+21 +101 +27,5 +14 +11 -11 -4	<0,01 <0,001 <0,001 0,001 0,001 0,05 0,02
Clyne et al. (1991)(139) SWEDEN	19	Exercise N=10 (63 ± 14,5) Control N= 9 (59 ± 12,3)	GFR≤ 15ml (min.1,73 m^2) No RCT	Interval EX 60-70% max EX capacity. Strength EX. 45 min. 3x/week	12	GXT workload Static endurance test Dynamic endurance test GFR	+9,4 +46,7 +120,9 -13,3	<0,01 <0,002 <0,001 NS
Deligiannis et al. (1999_b)(19) GREECE	60	Exercise N=30 (48 ± 12) Control N= 30 (48 ± 11)	ND RCT	10 min warming up 50 min callisthenics, aerobics, swimming, ball games 60-70% HR_{max} 20 min strength low R and stretching 10 min cooling-down 3-4x/week	24	$VO_{2\ peak}$ GXT duration HRV index SD of R-R interval R-R interval length N patients with HRV index <25 N patients with arrhythmias (low class>II)	+41 +33 +31 +18 +3,8 -40 -33	<0,05[a] <0,05[a] <0,05[a] <0,05[a] <0,05[a] <0,05[a] <0,05[a]
Deligiannis et al. (1999_a)(11) GREECE	38	Exercise 1 N=16 (46,4 ± 13,9)	ND RCT	90 min: warming-up, aerobics, strength exercise low R, stretching 60-70% HR_{max} 3x/week	24	Exercise 1 LV mass index Ejection fraction Stroke volume index Cardiac output index	 +11 +12 +23 +20	 <0,05[a] <0,01[a] <0,05[a] <0,05[a]
		Exercise 2 N=10 (51,4 ± 12,5) Control N=12 (50,2 ± 7,9)	HB	Cycle ergometer 30 min at 50-60% HR_{max} Stretching exercises >5x/week		Exercise 2 No significant adaptations vs. Control group		
DePaul et al. (2002)(29) CANADA	29	Exercise N=15 (55 ± 16) Placebo N=14 (54 ± 14)	ID RCT	Cycle 20 min RPE 13 <80% HR_{peak} Ex quadriceps, hamstrings 50% to 125% 5RM 3sets x 10 reps 3x/week	12	GXT workout Hamstrings + quadriceps strength 6MWT (no encourage) symptoms KDQ HRQoL - SF-36	+109,5 +37,3 +1 +2 No ↑	0,02[a] 0,02[a] NS NS NS
Kouidi et al. (1998)(34) GREECE	7	Exercise N=7 (44,1 ± 17,2) Years on HD (4,6 ± 4,1)	ND	10 min warming up 50 min aerobics (calisthenics, steps, swimming, ball games) 10 min strength lowR 10 min stretching 10 min cooling-down 3x/week	24	GXT duration VO_{2peak} Peak blood lactate Nerve conduction velocity Isometric strength Type I muscle fibre area type II muscle fibre area % of type II fibres	+28,8 +48 -16 +12,7 +48 +25,9 +23,7 +23	<0,05[b] <0,05[b] <0,05[b] <0,05[b] <0,05[b] <0,05[b] <0,05[b] <0,05[b]
Mercer et al. (2002) (140) UK	16	Exercise N=7 (63 ± 14,5) Control N= 9 (59 ± 12,3)	ND No RCT	15 min warming-up Cycle Intervals 3x5 min 72 ± 7% HR_{peak} RPE 13. 8 exercises muscular endurance 3 sets x 12 reps 2x/week	12	Total walk time Stair climb Stair descent Perceived walk speed Perceived leg weakness perceived breathlessness	-15 +22 +18 +15 +25 +32	≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a] ≤0,05[a]
Moros García et al. (1993)(97) SPAIN	8	Exercise N= 8 (51) HD time 38,2 months	ND	Cycling Circulatory exercises Abdominal strengthening Respiratory exercises 30-40 min	16	GXT duration GXT workout GHQ anxiety GHQ depression GHQ total	+19,48 +16,6 ↑ ↑ ↑	NS <0,05 <0,05 NS <0,05
Oh-Park et al (2002)(141) USA	18	Exercise N= 18 (52)	ID	Knee ext 3 sets x 15 reps 50% 1RM Cycle 70-85% HR_{peak} RPE <14, 30 min 2-3x/week	12	1 RM knee extension SF-36 PCS SF-36 MCS	+82 +24,7 +13	<0,0001 0,0003 0,004

Authors (year) Country	N	Study groups (age mean ± SD)	Exercise intervention			Outcomes		
			Delivery Design	prescription	weeks	Variable	%mean change	P
Painter et al. (2000_a)(78) USA Painter et al. (2000_b)(79) USA	216	Exercise (55,9 ± 15,1) HD months (33,7 ± 35,6) Control (52,8 ±16,8) HD months (40,2 ± 62,4)	HB ID noRCT	HB 8 weeks Flexibility 5-6x/week Strength 3x/week 3 sets x 15 reps. Walking/cycle 3-4x/week ID 8 weeks Cycle 30 min 3x/week	16	Habitual gait speed Fastest gait speed STS 10 (n=111) 6MWT (n=44) SF-36 PF (N=216) SF-36 role physical SF-36 general health SF-36 bodily pain SF-36 PCS SF-36 MCS	+3 +2 +24 +7,7 +12 +35 +9,1 +10,1 +9,1 +4,8	0,021[a] <0,001[a] 0,05[a] 0,05[b] 0,004[a] <0,001[a] 0,05[a] 0,003[a] <0,001[a] NS
Van Vilsteren et al. (2005)(117) USA	96	Exercise N=53 (52 ± 15) Control N=43 (58 ± 16)	ID RCT	Strength preHD 30-40' ↓ Resistance Cycle HD 20-30 min 60% max capacity Ex counselling TTM: cognitive-behavioural strategies to become active 3x/week	12	$VO_{2\ peak}$ STS-10 Reaction time SF-36 PF SF-36 Vitality SF-36 General Health Depression Kt/V Behavioural change	+10,1 -22,3 -11,1 +10,6 +23,3 +25,4 ↑ +5 ↑	NS 0,05[a] 0,002[a] NS <0,05[a] <0,05[a] NS <0,05[a] <0,05[a]

BP = Blood Pressure; **GFR** = Glomerular Filtration Rate; **GHQ** = General Health Questionnaire; **GXT** = Graded Exercise Test; **HB** = Home Based; **HD** = Hemodialysis; **HR_{max}** = Maximal Heart Rate; **ID** = Intra-dialysis; **HRQoL** = Health Related quality of life; **HRV** = Heart Rate Variability; **ID** = Intra-dialysis; **KDQ** = Kidney Disease Questionnaire; **LV** = Left Ventricle; PA = Physical Activity; **MCS** = Mental Component Scale; **min** = Minutes; **ND** = Non-dialysis time; **No RCT** = Nonrandomized Controlled Trial; **NS** = Nons significant; **PCS** = Physical Component Scale; **PF** = Physical Function; **R** = Resistance; **RCT** = Randomized Controlled Trial; **reps** = repetitions; **RM** = Resistance Maximum; **RPE** = Rate of Perceived Exertion; **SD** = Standard Deviation; **SF-36** = Medical Outcomes Survey Short Form; **STS** = Sit to Stand to Sit test; **TTM** = Transtheoretical; ↑ = Increase; **RPE** = Rate of Perceived Exertion; **6MWT** = Six Minutes Walking Test

[a] Significant change over time vs. comparison group.

[b] Significant vs. baseline values within group.

Therefore, we could conclude that most of the 1361 participants in exercise programs for ESRD patients have undertaken aerobic programs (Table IV) and have demonstrated beneficial effects on cardiorespiratory fitness. Only 15 out of 49 studies included a sample size above 30 subjects. Despite the diminished strength found in this cohort and the presence of lower limbs fatigue as the main exercise limiting factor, few studies on PRT programs have been performed. Concerning HRQoL and/or physical functioning, some of the studies on PRT or combined programs improved them. In the last decade, for first time, studies on HD patients over 60 years mean age were undertaken, probably due to the tendency of increased age in this cohort and to the previous knowledge of safeness and benefits of these programs for the most disabled patients (79).

Table IV. Summary of the literature reviewed

TYPE OF PROGRAM	AEROBIC	PROGRESSIVE RESISTANCE TRAINING	COMBINED	TOTAL
Number of Studies (Studies on PRE-HD)	28 (3)	9 (4)	12 (1)	49 (8)
USA	11	5	5	21
Greece	3	0	3	6
UK	4	0	1	5
Spain	3	1	1	5
Canada	2	0	1	3
Sweden	0	2	1	3
Denmark	2	0	0	2
Australia	0	1	0	1
Estonia	1	0	0	1
Korea	1	0	0	1
Turkey	1	0	0	1
Design				
RCT	15	4	3	22
Non-RCT	4	3	4	11
Uncontrolled trial	10	2	4	16
Interventions				
Intra-dialysis	12	3	5	20
Non-dialysis days	13	2	4	19
Home-based	2	1	2	5
Total patients	621	217	523	1361
Mean Sample size	24	28	53	-
1 to 10 patients	3	2	2	7
11 to 20 patients	10	2	4	16
21 to 30 patients	7	3	1	11
31 to 40 patients	5	0	1	6
41 to 50 patients	2	1	0	3
51 to 60 patients	1	0	1	2
61 to 70 patients	0	0	0	0
71 to 80 patients	0	1	0	1
>81 patients	0	0	3	3
Age of participants				
Youngest patient	27	43	44	-
Oldest patient	67	68	63	-
Number of studies with mean age ≥60/All studies	1/28	6/9	1/12	8/49

There is a gap in the literature on the effects of PRT programs. The implementation of this specific kind of exercise during HD was found only in 2 out of 48 studies reviewed , excluding a pilot study previous to this thesis presentation (137), and none of them found an impact on physical functioning tests (6MWT and STS). Besides, none of these two studies evaluated the impact of PRT on cardiorespiratory fitness. Finally, none of the RCT implementing PRT programs on HD patients included an exercise comparison group. Additionally, none studies on intradialytic exercise have been performed in Spain.

CHAPTER 2: AIMS AND HYPOTHESIS

The general aim of this study is to investigate the effect of a progressive resistance training (PRT) intradialysis program on a group of patients with mean age around 60 years old.

The specific aims of this study are:

- To investigate the effects of a PRT intradialysis program on exercise capacity.
- To investigate the effects of a PRT intradialysis program on strength and physical functioning.
- To investigate the effects of a PRT intradialysis program on HRQoL.
- To investigate if the inclusion of close chain strengthening exercises added to traditional open chain strengthening exercises produces additional benefits on activities of daily living of HD patients.
- To compare the relative effects of PRT versus low-intensity aerobic exercise training on exercise capacity, strength, physical functioning and HRQoL.

The hypotheses tested in the present study were that a PRT intradialysis program implemented during 6 months, compared to a low intensity aerobic exercise program, would:

- Improve exercise capacity (time and METS achieved on the GXT).
- Improve strength of knee extensor muscles.
- Improve results on the physical functioning tests (6MWT: meters walked in 6 minutes; STS-10: time to perform 10 repetitions from sit to stand position; and STS-60: number of repetitions in 60 seconds).
- Improve HRQoL, as measured by the SF-36 (8 scales and 2 components).

CHAPTER 3: METHODOLOGY

3.1. PATIENTS

This multicentric study included patients from Hospital General Universitario in Valencia (Spain) undertaking HD in two different HD clinics, Hospital General Universitario (11 patients) and Clínica Virgen del Consuelo (16 patients), recruited from December 2005 until January 2007. All patients attending HD were evaluated for eligibility via medical history review and authorization from the patient's nephrologist before solicitation of interest and written informed consent. Patients were included if they were in a stable condition under their medication and undertaking HD sessions for at least 3 months. Causes for not admission in the study were recent myocardial infarction (6 weeks), uncontrolled hypertension, malignant arrhythmias, unstable angina and any neurological, respiratory or musculoskeletal disorder that exacerbated by activity.

The study was carried out within the ethical standards set forth in the Helsinki Declaration of 1975. Ethical approval was obtained from both the Ethical Committee at the 'Fundación del Hospital General Universitario de Valencia' (Registry Number 2777) and the Research and Ethical Committee at the Universidad CEU-Cardenal Herrera (Registry Number 9809). Written informed consent was obtained from all participants.

3.2. DESIGN

At the beginning of the study all patients underwent clinical examination and a graded exercise testing to evaluate their exercise capacity and to detect possible contraindications to exercise on a non-dialysis day. Additionally, dynamometry was performed to assess their lower limbs' muscle strength, as well as simple functional tests on a different day. All tests were performed before the HD sessions on separate days. Finally, the SF-36 questionnaire was administered to all patients.

After initial evaluation, patients were randomly assigned via table of random numbers, stratified by age and gender, either to a progressive resistance (group A) or to a low level aerobic (group B) exercise training program. Since the aim of the study was to examine the effects of resistance training, the number of the subjects in the resistance-trained group was planned to be double compared to B. We came to this decision, also due to the availability of stationary cycles required for training of group B. Thus, 19 patients were included in group A and 8 in group B. Patients of group B were exercised aerobically with the minimum possible workload, instead of being sedentary, because it was thought to be unethical to exclude someone from the benefits of exercise. Participants were blinded to treatment assignment. Medications and dialysis schedule of participants were constant during the study. After the 6-month training period all measurements were repeated.

3.3. OUTCOMES

3.3.a. Sit to Stand to Sit Test (STS 10 and STS 60)

Both tests, which are used as indirect measures of lower limb muscle power and endurance (79,90), were performed before the second HD session of the week, following the procedure described in the literature (142). Verbal encouragement was provided in both tests. At the end of each of the tests the rate of perceived exertion (RPE, scale grading from 6 to 20) was recorded.

The STS 10 consisted of measuring the seconds employed by the patient to stand up from the sitting position, on a chair without arm rests with the arms kept across the chest, and to sit down for 10 consecutive times as quickly as possible. One trial was performed previous to the final measurement of the total time. STS-10 is proved to be a feasible measure to detect changes resulting from an exercise intervention (79).

After five minutes for recuperation, the patient performed the STS 60 keeping the same posture in the chair. It consisted of standing-up from the chair and sitting-down again as many times as possible during a 60 seconds-period and the number of repetitions were registered.

3.3.b. 6 Minutes Walking Test (6MWT)

It was used as an indicator of patients' exercise capacity (143). Subjects completed this test before the third HD session of the week, on a walk of 20 meters in

length along an internal corridor of the HD unit. The instructions given to the patients were to walk for 6 minutes along the 20 meters, turning on without stopping, as fast as they could, without running, feeling that they couldn't have walked faster. The total distance covered and the RPE were recorded. Patients were allowed to use walking aids or to stop and take a rest during the test if needed. Standard verbal encouragement and feedback on the remaining time was given to the subjects. Heart rate and blood pressure were measured at the beginning and the end of each test.

3.3.c. Dinamometry

Peak force (N) of the knee extensors was measured bilaterally (digital dynamometer GLOBUS Italia Tesys) on a different day of the functional tests, before the second HD session of the week, by three consecutive maximal isometric repetitions, and the best score was recorded. The patient sat so that the hip and knee remained at 90º flexion. The dynamometer's strength transductor was attached to the distal tibia and fibula keeping an angle of 90º with the tibial bone. Verbal encouragement was provided in order to obtain maximal strength.

3.3.d. Graded Exercise test (GXT)

Before starting the program, patients performed an evaluator-blinded exercise test on a treadmill the day before the third HD session of the week, according to Bruce protocol. Subjects were exercised until volitional exhaustion or the presence of symptoms, severe hypertension or hypotension, or ST-segment shift in ECG. Data on exercise time and METS (1 MET level of energy expenditure equal to 3.5 ml

O_2/kg/min) achieved were recorded. During the tests the ECG of each individual was monitored continuously and recorded at each stage, while the blood pressure was measured by sphygmomanometry.

3.3.e. Medical Outcomes Survey short form (SF-36)

The Spanish version of SF-36, which was translated and validated by Alonso et al. (120), was used to assess patients' Health Related Quality of Life (HRQoL). Its 36 items are compiled into eight scales: Physical Functioning (PF), Role Functioning-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Functioning-Emotional (RE) and Mental Health (MH). These scales are scored from 0 (worst health) to 100 (best health). Normalized scores representing overall physical functioning and mental functioning are calculated from the individual scales and are represented as the physical component scale (PCS) and the mental component scale (MCS). The PCS includes the scales of PF, RP, BP, GH, VT and SF. The MCS is composed of the scales RE, MH, GH, VT and SF. The component scale scores are normalized to a general population mean of 50 and standard deviation of 10. The questionnaire was completed during dialysis in an interview-schedule assisted by the study staff.

3.3.f. Dry weight, Blood Pressure, KtV and Hematologic Assessments

Dry weight, blood pressure and KtV were measured routinely at each dialysis session. For calculation of body mass index (BMI) body weight was measured before starting HD, and the dry weight at the last week of the month was considered for

analysis. Concerning blood pressure and KtV, the mean values of every HD session during a whole month were calculated. Systolic and diastolic blood pressure measurements were made in the arm while sitting immediately after starting the HD session. Blood samples for measurements of hematocrit and hemoglobin, blood albumin, urea, glucose, serum creatinine, HDL-cholesterol, LDL-cholesterol, triglycerides, total cholesterol, potassium, sodium, calcium, phosphate and PTH were measured routinely monthly.

3.4. INTERVENTION

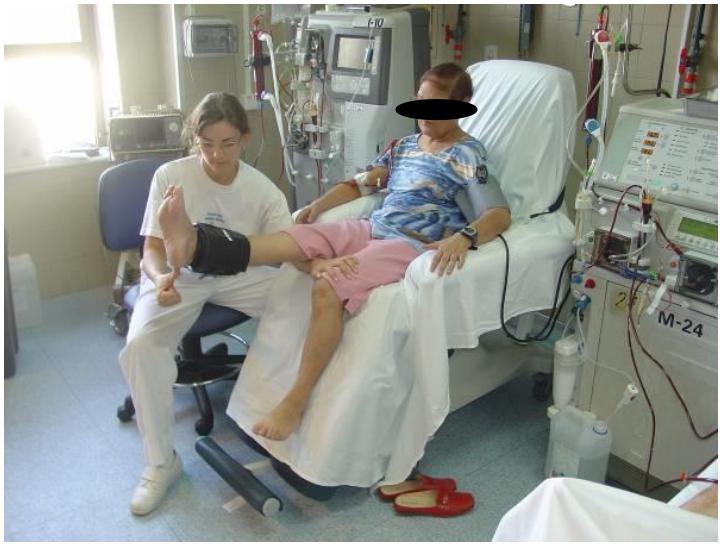
Patients of both groups were exercised under the supervision of a physiotherapist during the first 2 hours of the 3 routine HD treatments per week, for a period of 6 months. All exercises were performed on a seated or supine position. Warm-up and cool-down phases of the exercise sessions were common to both groups, and consisted of 5 minutes stretching exercises for triceps sural, hamstrings, and external rotator muscles of the hip. Main exercise phase lasted 25 minutes and differed between groups.

MAIN PHASE GROUP A: It consisted of 4 progressive isotonic and isometric resistance exercises that specifically targeted major muscle groups of the lower extremities. First exercise (Photography 1) consisted of extending one knee from a standardized position 90º flexed knee until 0º keeping limb horizontal, with attached weights applied to the ankle. Second exercise consisted of unilateral triple extension (hip, knee and ankle) against the physiotherapist. Patient was asked to perform a triple extension from a standard position with hip and knee bent 90º. Both exercises progressed by increasing resistance so that the patient could perform 3 sets of 15

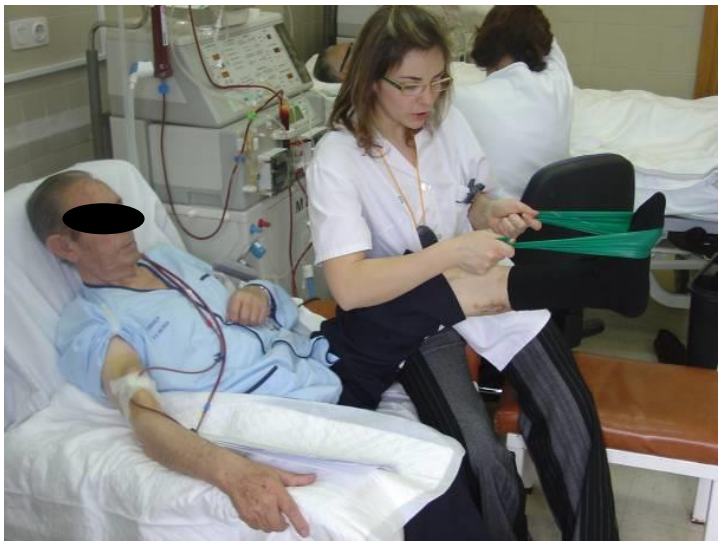
repetitions. Third exercise (Photography 2) consisted of unilateral triple extension against an elastic band. Position was standardized at 90º knee flexion, and the elastic band length remained unchanged and was fixed at metacarpal heads level of the shoes. Progression was adjusted by double elastic band, and patient performed 1 set of 15 repetitions. Last exercise consisted of contracting ankle flexor muscles, quadriceps and hip extensor muscles isometrically (Photography 3). Patient was asked for a bilateral maximal contraction from a standardized hip position, knee extended and ankle dorsiflexed. Progression was performed by increasing contraction time up to 6 seconds, and patients performed 1 set of 15 repetitions. Proper breathing technique was emphasized during all exercises to avoid Valsalva maneuver, as recommended by previous research (144).

The intensity for all the exercises was adjusted via the RPE at a level between 12 and 14, so that the patient did not feel the exercise 'hard' (not more than 15 at the RPE) nor 'somewhat light' (not less than 11 at the RPE).

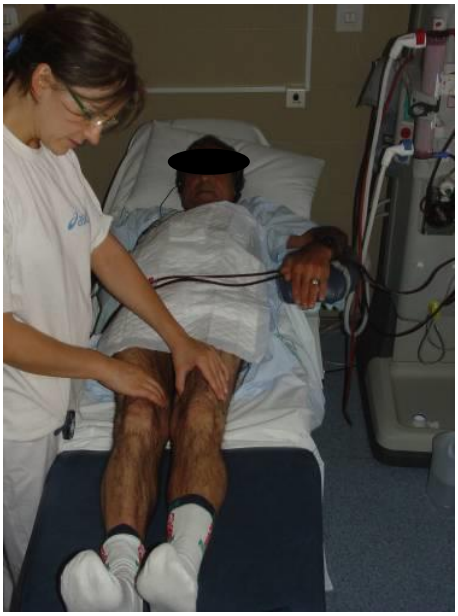
Photography 1. Knee Extension Exercise



Photography 2. Triple Extension Exercise



Photography 3. Isometric Exercise



MAIN PHASE GROUP B: It consisted of exercise with a stationary cycle (Mottomed Letto) at a constant low workload, so that the intensity was equivalent to an RPE of 11 (fairly light: light exercise).

3.5. ADHERENCE TO EXERCISE PROGRAM

Adherence to treatment was defined as the number of sessions performed divided by the number of sessions offered, multiplied by 100. Subjects were included in the analyses if they performed, at least, 50% of the sessions offered.

3.6. STATISTICAL ANALYSIS

The optimal sample size was calculated based on hypothesized differences between groups A and B to perform the STS 10. On the basis of previous studies (117), group B (low level aerobic training) was estimated to have no change, whereas group A (progressive resistance training) was hypothesized to decrease 6 seconds in the STS 10 with a SD of 7 seconds. Using a one-tailed test of significance and setting the α at 0,05 and to have a 80% chance of detecting difference, a total of 18 patients per group (36) were estimated to be required. Nevertheless, due to poor recruitment (Figure 1, high number of non-participants), only 27 patients were finally included in the study.

Data distribution was checked both visually and statistically (skewness and kurtosis) before describing and analysing the sample. Mean and standard deviation were computed where appropriate. For the analysis of outcomes between groups before and after intervention, a two-way repeated-measures ANOVA was applied, with group and time as predictor variables. This parametric test was used despite lack of normal distribution, because the nonparametric equivalent (Friedman's test for nonparametric randomized repeated measures ANOVA) in our study characterized by the factor presenting two levels has a power of only 64% of the parametric test (145). If significant time effect was found on two-way ANOVA repeated measures analysis

($p \leq 0,1$), the intra-group analysis between pre and post-intervention values in both groups was performed by the Wilcoxon Signed Ranks Test (not normal distribution) or by the Student T test for paired samples. Statistical analysis was performed using SPSS 15.0 for Windows.

CHAPTER 4: RESULTS

4.1. STUDY PATIENTS

From a total of 59 patients, 34 volunteered to participate in the study (Figure 1). After initial evaluation 7 patients were excluded from the study for medical reasons, since they did not meet the inclusion criteria. The rest 27 were randomly assigned into two groups. During the 6 months, 2 patients of group A dropped out of the study, one due to lower limb amputation and one due to lack of interest and were excluded from the analysis. Three other patients did not perform some of the tests due to acute musculoskeletal problem on the arm and worsening medical condition, so available post-intervention data were included in the analysis. Characteristics of the 25 participants, who completed the study, are shown in Table V. Overall, the sample was composed of 17 men and 8 women. There were no significant differences in baseline patient characteristics across study groups.

Adherence of patients to the program was defined as the percentage of sessions completed from scheduled sessions. The mean attended sessions was 80,1 % for group A and 87,9% for group B. The inter-groups analysis showed no statistically significant difference. There were no complications due to exercise training during the study period.

Figure 1. Participants Flowchart

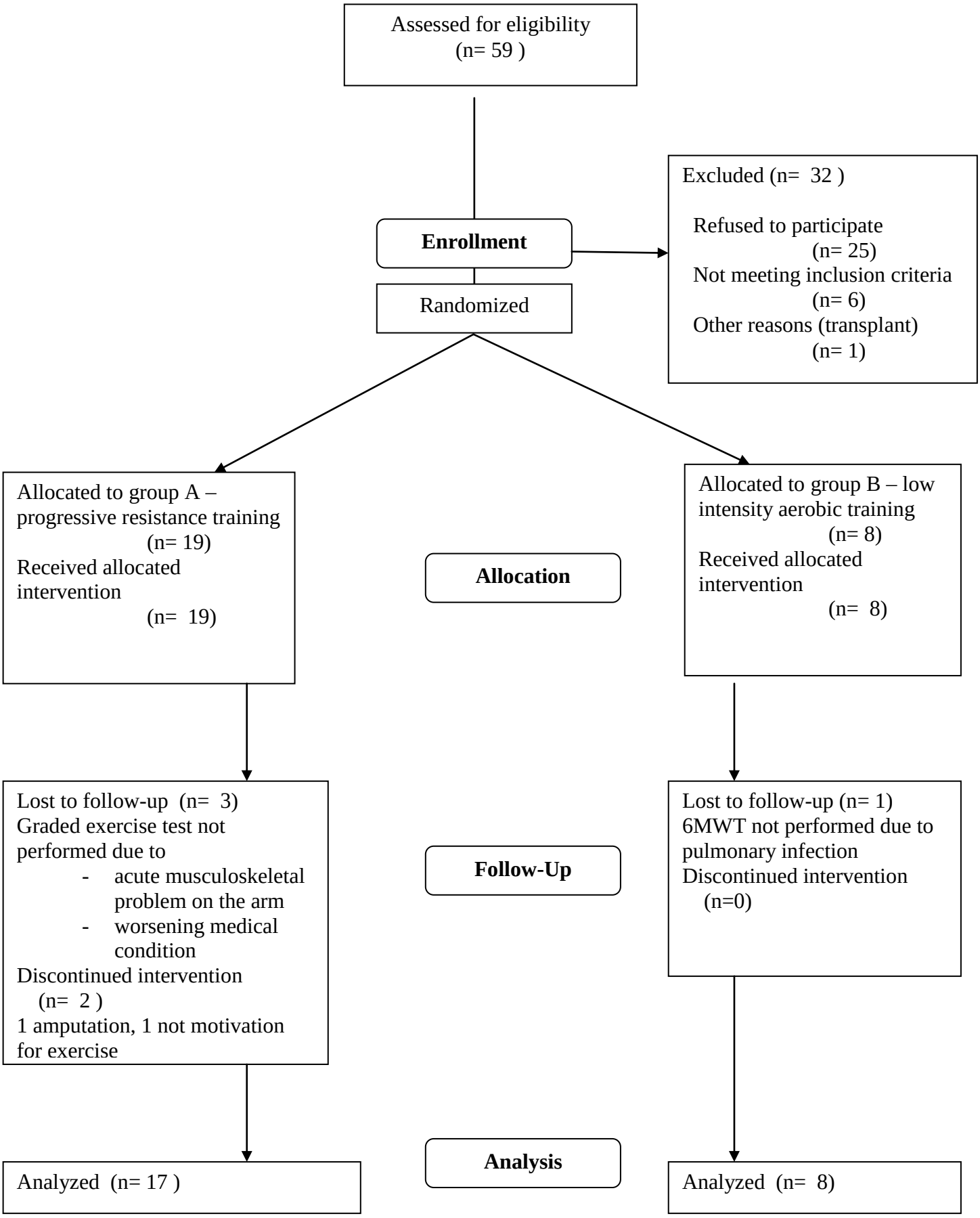


Table V – Patient characteristics

VARIABLE	Group A (n=17)	Group B (n=8)	p
AGE (years)	53,5 ± 18,0	60,1 ± 16,9	0,281
GENDER, male/female	11/6	7/1	0,364
COMMORBIDITY (number of illnessess)	2,6 ± 1,2	3,4 ± 0,9	0,368
DRY WEIGHT (Kg)	64,9 ± 13,0	72,4 ± 7,8	0,162
BODY MASS INDEX (Kg/m2)	24,6 ± 2,6	24,9 ± 2,2	0,540
HEMODIALYSIS VINTAGE (months)	37,3 ± 34,9	53,7 ± 42,0	0,382
HEMODIALYSIS PER WEEK (hours)	12,0 ± 2,1	12 ± 0	0,558
Kt/v	1,2 ± 0,3	1.3 ± 0,1	0,114
HEMOGLOBINE (g/dL)	12,0 ± 2,0	12,3 ± 0,8	0,162

Values presented as mean ± SD. Continuous values analysed by the Mann Whitney Test. Proportions analysed by Fisher's Exact Test

4.2. PHYSICAL FUNCTIONING, GRADED EXERCISE TEST AND DYNAMOMETRY

At baseline, time to perform the STS 10 on group A was by 15,7% lower than group B, although the difference was not statistically significant (Table VI; Figure 2-4). Similarly, meters on the 6MWT in group A were by 13,7% (NS) less than in group B. Concerning STS 60, group A performed at baseline by 4,2% (NS) more repetitions compared to group B. No differences were noted in change over time between groups A and B in the STS 10, STS 60 and 6MWT. Intragroup analysis showed that Group A decreased the time to perform STS 10 by 22,3 % ($p<0.05$), while group B only by 6,4 % (NS). Thus, group A increased from the 54,6 % to 87,1 % ($p<0.05$) of the predicted normal values (142), whereas group B increased from the 78,3% to 86,0% (NS). Concerning STS 60, group A increased the number of repetitions by 17,7 % ($p<0.05$), while group B by 2,2 % (NS). Additionally, group A increased the distance walked on the 6MWT by 11,2 % ($p<0.05$), while group B by 8,9 % (NS).

Table VI – Changes in Physical Functioning from baseline to 6 months

VARIABLE	Group A	Group B	N	F TIMExGROUP	P[a]	F TIME	P[b]
STS-10 (seconds)							
PRE	24,2 ± 13,2	20,4 ± 3,3					
POST	18,8 ± 7,9	19,1 ± 2,7					
Change	-5,4 ± 10,6 ‡	-1,3 ± 3,5	25	1,131	0,299	2,991	0,097
STS-60 (repetitions)							
PRE	28,8 ± 11,2	27,6 ± 8,1					
POST	33,9 ± 12,6	28,2 ± 7,6					
Change	5,1 ± 5,8 *	0,6 ± 7,1	25	2,818	0,107	4,404	0,047
6MWT (meters)							
PRE	432,5 ± 109,3	491,7 ± 87,3					
POST	481,0 ± 100,3	535,7 ± 77,3					
Change	48,5 ± 60,8 †	20,6 ± 36,6	24	1,267	0,272	7,743	0,011

PRE – Pre-intervention; POST – Post-intervention; STS- Sit to Stand to Sit Test; 6MWT-6 Minutes Walking Test
Values presented as mean ± SD
Analysis was by two way ANOVA repeated measures. P^a values are for the interaction between time and the intervention. P^b values are for pre-post intervention time effect
Intragroup comparison between pre-intervention and post-intervention:
‡ P = 0,003 Analysis by Wilcoxon Signed Ranked Test because of no normal distribution of data
† P = 0,003Analysis by T Test related samples because of normal distribution of data
* P= 0,0005 Analysis by Wilcoxon Signed Ranked Test because of no normal distribution of data

Figure 2. Results of Sit to Stand to Sit 10 Test. (■) Group A – progressive resistance training, (♦) Group B – low intensity aerobic training. P are for interaction of group over time. Values expressed as mean. Abbreviation NS not significant

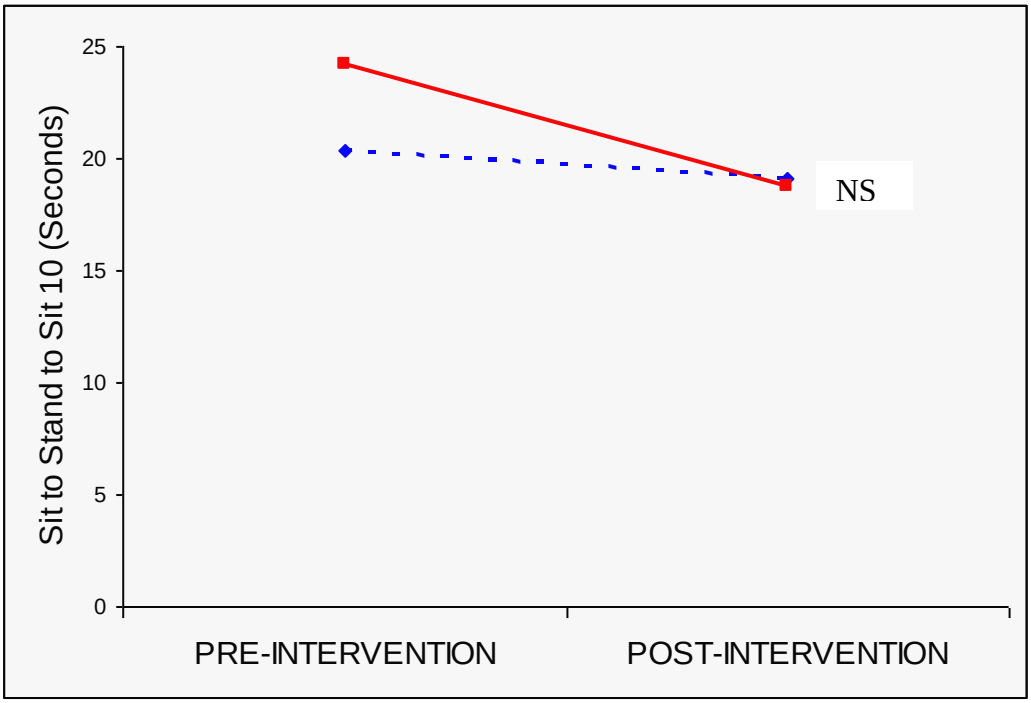


Figure 3. Results of Sit to Stand to Sit 60 Test. (■) Group A – progressive resistance training, (♦) Group B – low intensity aerobic training. P are for interaction of group over time. Values expressed as mean. Abbreviation NS not significant

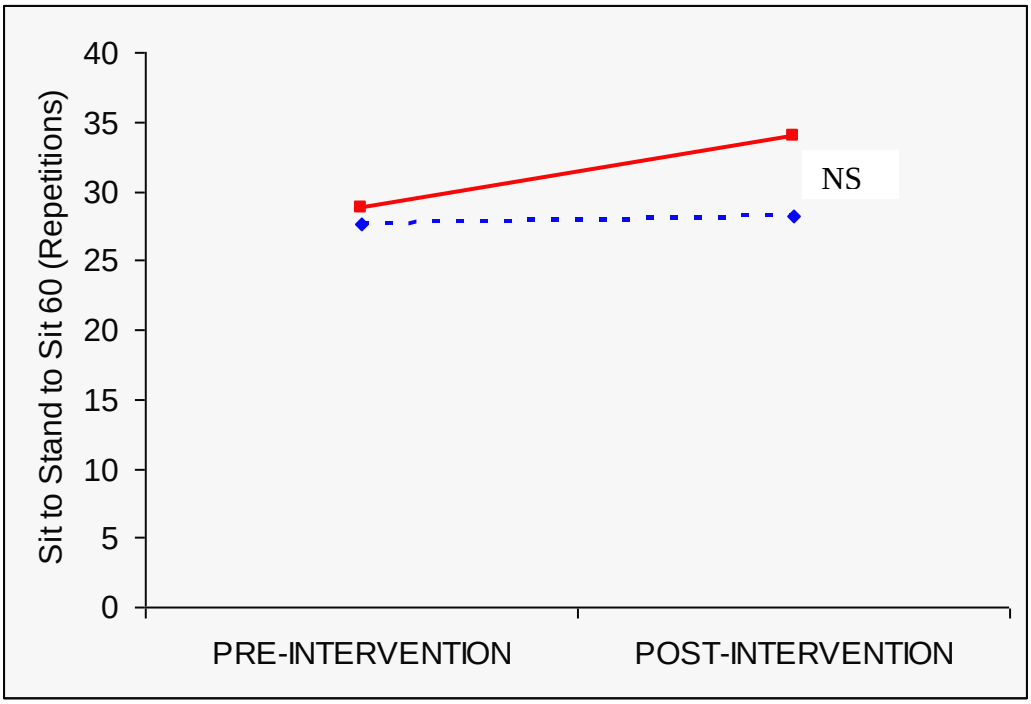
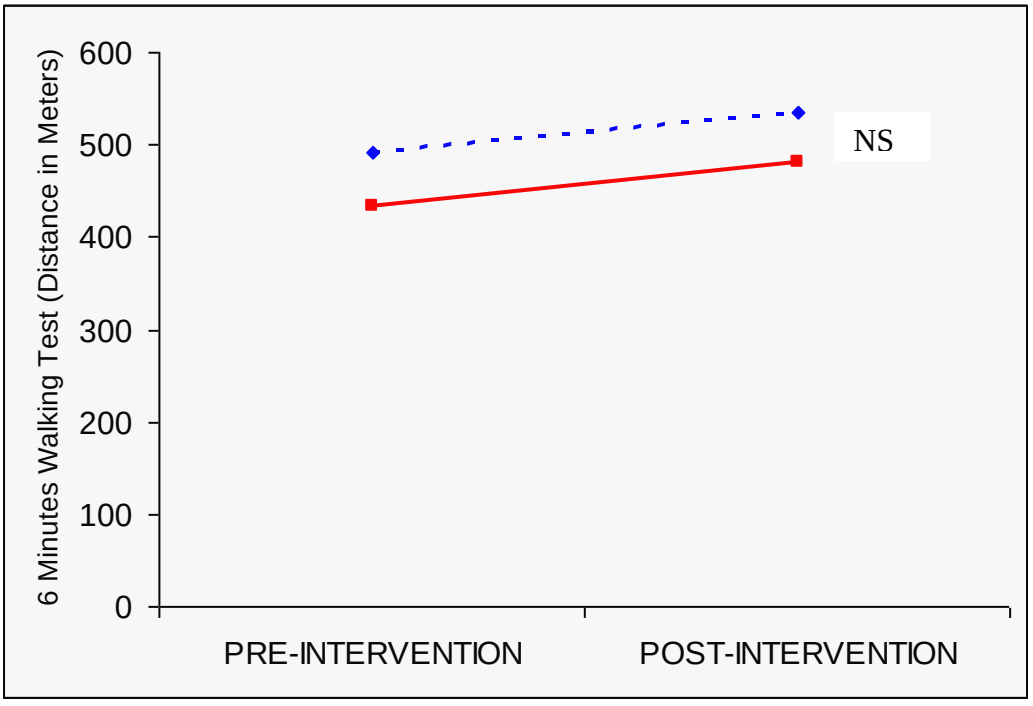


Figure 4. Results of Six Minutes Walking Test. (■) Group A – progressive resistance training, (♦) Group B – low intensity aerobic training. P are for interaction of group over time. Values expressed as mean. Abbreviation NS not significant



Baseline comparison between groups in terms of time and METS achieved on the GXT showed no significant differences (Table VII). Group A achieved at baseline by 8,2% (NS) less time and by 10,5% (NS) less METs compared to B. No differences were noted in change over time between groups in terms of time and METs achieved on the GXT. At the end of the study Group A showed a significant improvement in METs by 15,8 % ($p<0.05$), while group B achieved only a 6,3 % (NS) increase.

Table VII – Changes in Graded Exercise Test and Dynamometry from baseline to 6 months

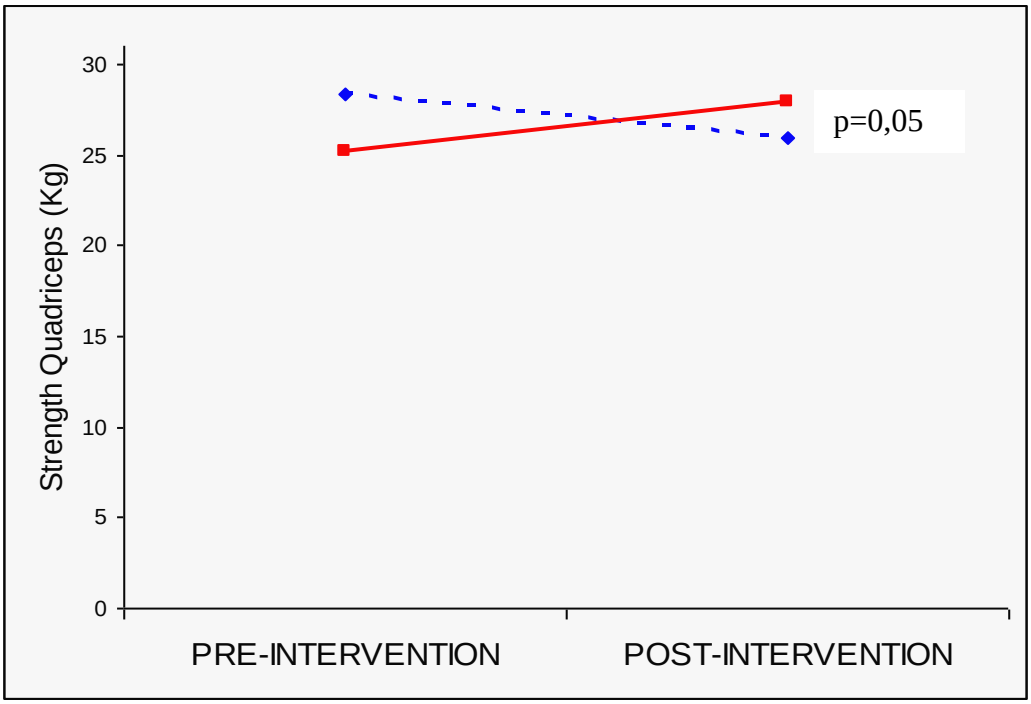
VARIABLE	Group A	Group B	N	F TIMExGROUP	P[a]	F TIME	P[b]
Graded Exercise Test							
Time (minutes)							
PRE	4,9 ± 2,3	5,3 ± 3,8					
POST	5,8 ± 2,7	5,7 ± 3,2					
Change	1,0 ± 1,8	0,3 ± 1,6	17	0,607	0,448	2,357	0,146
METS							
PRE	5,7 ± 2,0	6,3 ± 3,6					
POST	6,6 ± 2,7	6,7 ± 3,1					
Change	0,9 ± 1,9 *	0,4 ± 1,5	22	0,321	0,578	2,952	0,101
Dynamometry							
Right leg (Kg)							
PRE	25,2 ± 9,3	28,4 ± 9,4					
POST	27,9 ± 9,4	26,0 ± 9,5					
Change	1,5 ± 4,2	-2,3 ± 4,8	24	3,979	0,050	0,205	0,655
Left leg (Kg)							
PRE	25,4 ± 10,2	26,2 ± 9,3					
POST	28,0 ± 10,1	26,7 ± 8,6					
Change	1,2 ± 4,6	0,5 ±5,3	24	0,133	0,719	0,645	0,431

PRE – Pre-intervention; POST – Post-intervention
Values presented as mean ± SD
Analysis was by two way ANOVA repeated measures. P^a values are for the interaction between time and the intervention. P^b values are for pre-post intervention time effect
Intragroup comparison between pre-intervention and post-intervention:
* P= 0,043 Analysis by Wilcoxon Signed Ranked Test because of no normal distribution of data

As shown at Table VII, at baseline, group A showed by 12,7% (NS) lower values on dynamometry of the right leg and by 3,1% (NS) on the left leg compared to group B. At the end of the study dynamometry of the right leg showed a 5,9 % (NS) increase in group A and an 8,1% (NS) decrease in group B. Similarly were the results of the left leg dynamometry. Specifically, group A increased the maximal strength by 4,7

% (NS), while group B only by 1,9 % (NS). The test of the group by time interaction of the repeated-measures ANOVA in the right leg dynamometry indicated that the change over time was different between the groups ($F_{1,24}$ = 3,979; P= 0,05; Figure 5). Although left leg strength increased in both groups, none of these changes reached statistical significance, and there was a wide variation among patients.

Figure 5. Results of strength tests right leg. (■) Group A – progressive resistance training, (♦) Group B – low inensity aerobic training. P are for interaction of group over time. Values expressed as mean.



4.3. HEALTH RELATED QUALITY OF LIFE (SF-36)

Changes in the eight scales of the SF-36 and the PCS and MCS are shown in Table VIII and Figure 6. Baseline characteristics of the samples showed a lower level of the PCS (by 10,8%, NS) and the MCS (by 11,7%, NS) in group A compared to B. There was no difference noted in change over time between groups in any of the subscales, both the PCS and the MCS.

Figure 6. Results of Health Related Quality of Life (HRQoL) SF-36. Physical Component Scale (PCS) and Mental Component Scale (MCS). (■)Group A – progressive resistance training PCS, (□) Group A – progressive resistance training MCS (♦) Group B – low intensity aerobic training PCS, (○) Group B – low intensity aerobic training MCS . P are for interaction of group over time. Values expressed as mean. Abbreviation NS not significant

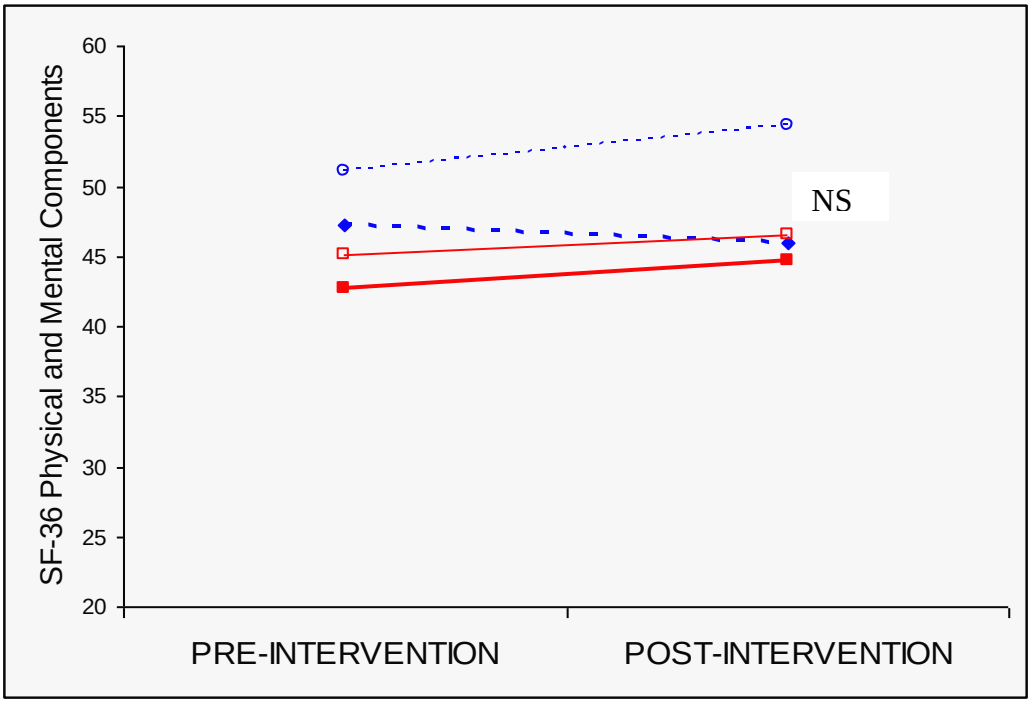


Table VIII – Changes in SF-36 components and subscales from baseline to 6 months

VARIABLE	Group A	Group B	N	F TIMExGROUP	P[a]	F TIME	P[b]
Subscales							
Physical Function							
PRE	67,9 ± 21,0	80,6 ± 20,9					
POST	79,1 ± 13,2	79,4 ± 19,9					
Change	9,4 ± 18,2	-1,2 ± 7,4	24	2,461	0,131	1,439	0,243
Role Physical							
PRE	69,1 ± 31,3	75,0 ± 40,1					
POST	73,4 ± 30,9	68,7 ± 45,8					
Change	0,0 ± 39,8	-6,2 ± 51,3	24	0,109	0,745	0,109	0,745
Bodily Pain							
PRE	68,3 ± 22,2	96,0 ± 7,4					
POST	65,7 ± 25,8	81,1 ± 23,8					
Change	-4,3 ± 25,9	-14,9 ± 26,8	24	0,866	0,362	2,859	0,105
General Health							
PRE	42,1 ± 20,7	50,0 ± 20,0					
POST	42,5 ± 22,5	61,5 ± 17,0					
Change	0,9 ± 27,4	11,5 ± 10,7	24	1,084	0,309	1,504	0,233
Vitality							
PRE	53,5 ± 20,6	66,2 ± 19,8					
POST	62,8 ± 19,7	73,7 ± 16,0					
Change	8,7 ± 25,0	7,5 ± 20,7	24	0,015	0,904	2,508	0,128
Social Function							
PRE	72,1 ± 27,1	82,8 ± 23,1					
POST	78,1 ± 27,6	87,5 ± 17,7					
Change	4,7 ± 22,8	4,7 ± 17,6	24	0,000	1,000	1,037	0,320
Role Emotional							
PRE	66,7 ± 44,1	95,8 ± 11,8					
POST	70,8 ± 41,9	95,8 ± 11,8					
Change	0,0 ± 45,5	0,0 ± 17,8	24	0,000	1,000	0,000	1,000
Mental Health							
PRE	69,2 ± 9,2	74,5 ± 17,6					
POST	69,5 ± 17,0	78,5 ± 14,3					
Change	-0,25 ± 17,2	4,0 ± 19,1	24	0,303	0,587	0,236	0,632
PCS							
PRE	42,7 ± 8,4	47,3 ± 6,9					
POST	44,7 ± 8,7	45,9 ± 8,7					
Change	1,4 ± 9,6	-1,4 ± 6,1	24	0,583	0,453	0,000	0,986
MCS							
PRE	45,1 ± 9,7	51,1 ± 8,9					
POST	46,5 ± 13,5	54,3 ± 5,1					
Change	0,7 ± 10,0	3,2 ± 8,5	24	0,348	0,561	0,896	0,354

PRE – Pre-intervention; POST – Post-intervention; PCS- Physical Component Scale; MCS- Mental Component Scale

Values presented as mean ± SD

Analysis was by two way ANOVA repeated measures. P^a values are for the interaction between time and the intervention. P^b values are for pre-post intervention time effect

4.4. CHANGES IN DRY WEIGHT, BMI, BLOOD PRESSURE AND KTV

At baseline, both groups were similar in terms of dry weight, BMI, blood pressure and KtV. Changes are shown in Table IX. No differences were noted in change over time between groups in dry weight (Group A increased 0,5%; Group B decreased 0,7%), BMI (Group A increased 0,4%; Group B decreased 0,8%) and KtV (Group A increased 8,3%; Group B no change). Systolic blood pressure increased by 2,6% in group B and decreased by 6,3% in group A, but no significant differences in change over time between groups were found. Similarly, diastolic blood pressure was found to increase by 2,9% in group B and decrease by 6,3% in group A, without achieving significant differences in change over time between groups.

Table IX – Changes in Dry weight, BMI, Blood Pressure and KtV from baseline to 6 months

VARIABLE	Group A	Group B	N	F TIMExGROUP	P[a]	F TIME	P[b]
Dry weight (Kg)							
PRE	64,9 ± 13,0	72,4 ± 7,8					
POST	66,1 ± 12,4	71,9 ± 8,1					
Change	0,3 ± 1,6	-0,5 ± 3,0	23	0,735	0,401	0,046	0,832
BMI (Kg/m^2)							
PRE	24,2 ± 2,8	24,9 ± 2,2					
POST	24,2 ± 3,0	24,7 ± 1,8					
Change	0,1 ± 0,6	-0,2 ± 1,0	25	0,733	0,402	0,161	0,692
Blood Pressure (mmHg)							
Systolic							
PRE	141,2 ± 18,2	135,9 ± 19,5					
POST	135,9 ± 23,2	139,5 ± 11,8					
Change	-5,3 ± 18,6	3,6 ± 22,9	23	1,014	0,326	0,035	0,854
Diastolic							
PRE	79,6 ± 11,9	73,5 ± 8,9					
POST	74,8 ± 11,9	75,6 ± 9,1					
Change	-5,0 ± 10,0	2,1 ± 11,2	23	2,458	0,132	0,400	0,534
KtV							
PRE	1,2 ± 0,3	1,3 ± 0,1					
POST	1,3 ± 0,3	1,3 ± 0,1					
Change	0,1 ± 0,2	0,0 ± 0,1	23	2,403	0,136	0,243	0,627

PRE – Pre-intervention; POST – Post-intervention ; BMI – Body Mass Index
Values presented as mean ± SD
Analysis was by two way ANOVA repeated measures. P[a] values are for the interaction between time and the intervention. P[b] values are for pre-post intervention time effect

4.5. CHANGES IN HEMATOLOGICAL ASSESSMENT

Changes for all variables analysed are shown in Table X. Only hemoblobin (Group A decreased by 1,7%; Group B increased by 15,1%; $F_{1,24} = 5,421$; P= 0,029) and hematocrit (Group A decreased by 2,5%; Group B increased by 15,9%; $F_{1,24} = 6,379$; P= 0,019) achieved statistical difference in change over time between groups. Additionally, ANOVA showed a significant time effect for both hemoglobin ($F_{1,24} = 3,609$; P= 0,07) and hematocrit ($F_{1,24} = 3,071$; P= 0,093). Despite no significant group per time interaction, a significant time effect was found on sodium (Group A decreased by 0,6%; Group B decreased by 2,3%; $F_{1,23} = 5,466$; P= 0,029) and PTH (Group A decreased by 23,5%; Group B decreased by 37,8%; $F_{1,21} = 7,610$; P= 0,012).

Table X – Changes in Hematologic Assessments from baseline to 6 months

VARIABLE	Group A	Group B	N	F TIMExGROUP	P[a]	F TIME	P[b]
Hemoglobine (g/dL)							
PRE	11,9 ± 2,0	10,6 ± 1,4					
POST	11,8 ± 1,0	12,2 ± 0,7					
Change	-0,2 ± 2,0	1,6 ± 1,2	25	5,421	0,029	3,609	0,07
Hematocrit (%)							
PRE	35,6 ± 5,8	31,4 ± 3,9					
POST	34,7 ± 3,4	36,4 ± 2,1					
Change	-0,9 ± 6,1	5,0 ± 3,5	25	6,379	0,019	3,071	0,093
EPO (Units per week)							
PRE	17235,3 ± 19794,3	13625,0 ± 8158,0					
POST	11666,7 ± 8853,3	12750,0 ± 8293,0					
Change	-6866,7 ± 22535,3	-875,0 ± 6875,2	24	0,529	0,475	0,883	0,358
Albumina (mg/dL)							
PRE	3,6 ± 0,5	3,6 ± 0,2					
POST	3,6 ± 0,4	3,6 ± 0,2					
Change	-0,3 ± 0,9	0,0 ± 0,2	21	0,092	0,765	0,019	0,892
Urea (mg/dL)							
PRE	152,8 ± 32,2	156,6 ± 31,7					
POST	153,1 ± 30,6	148,7 ± 35,4					
Change	0,3 ± 29,7	-7,9 ± 25,7	25	0,444	0,512	0,386	0,540
Glucose (mg/dL)							
PRE	98,5 ± 40,6	111,6 ± 28,7					
POST	99,2 ± 37,8	104,4 ± 19,2					
Change	0,8 ± 46,9	-7,2 ± 31,4	25	0,191	0,666	0,125	0,727
Serum Creatinine (mg/dL)							
PRE	9,5 ± 2,8	9,5 ± 2,9					
POST	9,6 ± 3,3	9,1 ± 2,5					
Change	0,1 ± 1,5	-0,4 ± 1,4	25	0,659	0,425	0,106	0,747
HDL-Choleterol (mg/dL)							
PRE	41,7 ± 14,0	34,1 ± 6,4					
POST	43,1 ± 16,0	35,7 ± 8,2					
Change	4,1 ± 16,8	3,2 ± 8,2	20	0,031	0,863	0,599	0,449
LDL-Choleterol (mg/dL)							
PRE	93,6 ± 39,1	76,2 ± 42,6					
POST	103,9 ±61,3	72,2 ±22,1					
Change	29,2 ± 64,8	19,2 ± 52,6	15	0,773	0,395	0,674	0,426
Triglycerides (mg/dL)							
PRE	141,3 ± 76,5	133,1 ± 121,5					
POST	176,8 ± 94,8	160,5 ± 66,0					
Change	12,6 ± 78,2	-25,2 ± 110,0	20	0,027	0,871	0,154	0,699
Total Colesterol (mg/dL)							
PRE	148,6 ± 49,2	134,0 ± 25,1					
POST	177,7 ± 63,1	141,5 ± 28,0					
Change	27,6 ± 51,7	7,3 ± 20,8	22	0,846	0,369	2,518	0,128
Potassium (mmol/L)							
PRE	5,6 ± 0,9	5,1 ± 0,6					
POST	5,5 ± 0,6	5,5 ± 0,8					
Change	-0,1 ± 0,9	0,4 ± 0,8	25	1,986	0,172	0,577	0,455
Sodium (mmol/L)							
PRE	141,7 ± 1,2	141,7 ± 1,2					
POST	137,6 ± 3,8	138,5 ± 2,7					
Change	-0,9 ± 4,5	-3,2 ± 2,8	24	1,812	0,192	5,466	0,029
Calcium (mgl/dL)							
PRE	9,8 ± 0,7	9,8 ± 0,7					
POST	9,0 ± 0,6	9,7 ± 0,6					
Change	-0,1 ± 0,6	-0,1 ± 0,5	24	1,247	0,276	0,002	0,962
Phosphate (mgl/dL)							
PRE	4,0 ± 1,3	4,0 ± 1,3					
POST	4,9 ± 1,9	3,8 ± 0,6					
Change	0,7 ± 1,1	-0,1 ± 1,3	25	2,659	0,117	1,052	0,316
PTH (pg/mL)							
PRE	523,9 ± 309,0	523,9 ± 309,0					
POST	425,1 ± 469,9	392,5 ± 231,9					
Change	-123,2 ± 283,3	-198,1 ± 168,8	22	0,414	0,527	7,610	0,012

PRE – Pre-intervention; POST – Post-intervention
Values presented as mean ± SD
Analysis was by two way ANOVA repeated measures. P^a values are for the interaction between time and the intervention. P^b values are for pre-post intervention time effect

CHAPTER 5: DISCUSSION

This study demonstrates that this inexpensive 24-week intradialytic progressive resistance training program results in statistically significant improvement in physical functioning, as measured by physical performance tests, leg strength and exercise capacity, without affecting patients' quality of life to a statistically significant degree. It is proved that properly screened dialysis patients are able to engage safely in an intradialytic program of resistance training, since there was no musculoskeletal, vascular access or hemodynamic complication as a result of the exercise intervention.

5.a. Six minutes walking test

At baseline, all HD patients showed decreased walking capacity, as it was assessed by the 6MWT. This result is consistent with the findings of previous studies that analysed walking capacity by the 6MWT in HD patients (29,78,114-116,123,126,136,137) compared to healthy counterparts (116) or predialysis patients (123). However, comparing the results of the 6MWT achieved by the HD patients in the different studies, there is a variety of almost 200 meters. The mean distance walked in 6MWT in our study was considerably higher than in the one reported by Painter et al. (78) in patients aged around 50 years, and lower than the one reported by Headley et al. (115) and Nindl et al. (136) reported in patients around 40 years old.

After the completion of the resistance training program the distance walked significantly increased. The apparent improvement in the 6MWT, of 48 m, is in

agreement with the results of previous studies, where the improvement ranges from 24 to 78 m (78,115,116,126,136,137). This improvement can be attributed to the morphological and functional skeletal muscle and neural adaptations to resistance training (146). However, two studies did not observe any statistically significant increase in the 6MWT after an exercise intervention (29,114). Cheema et al. (114) focused on maximal strength (8 to 10 repetitions per 2 sets) and implemented a full body program that included 5 exercises for lower limbs, and 5 exercises for upper limbs, working during 45 minutes per session, at intensities rating from 15 to 17 ('hard' to 'very hard') at the RPE. Considering that some exercises (supine hip flexion, supine straight-leg raise, bilateral leg raises) increase intradiscal pressure (123,127,147), patients could have overestimated perceived effort. Additionally, in the study by Cheema et al. (114) close chain exercises were not included. This discrepancy can partly be explained by the fact that patients in these studies had higher baseline values. Other possible explanation is the exercise training prescription. Factors that could explain the significant impact on walking capacity of our program are the length of the study, the high volume of our program (intermediate intensity (29,106,115,117,125) and high number of repetitions) working on muscular endurance, and the inclusion of close chain exercises that specifically reproduce movements performed in activities of daily living, such as walking, sitting up from a chair and climbing stairs. The 6MWT is a test of endurance (82) that has been used to document functional status of patients with congestive heart failure (148), chronic obstructive pulmonary disease (148) and chronic renal failure (143). Our findings support the usefulness of this test in HD population.

5.b. Sit to Stand to Sit Tests

In the STS 10 at baseline our patients achieved only the 55% of the expected values for healthy population. Moreover, baseline repetitions achieved on the STS 60 in the present study were low. Tests measuring functional tasks such as sitting up and down from a chair (STS) have been found to be impaired in HD patients compared to healthy counterparts in all studies reviewed (78,90,115,117,126,136-138,142). After the intervention, the improvement of 5,4 seconds on performance time is in agreement with the results found in previous studies, where the improvement ranges from 2,5 to more than 6 seconds (78,115,117,126,136,137). Additionally, the increase on 5 repetitions found on the STS 60 after resistance training was equivalent to the improvement found in previous studies (90,137,138). Only a previous study by Johansen et al. (121) on the effects of resistance training on STS did not find statistical significant improvement. They used the STS 5 (time to achieve 5 repetitions) and despite the inclusion of 5 exercises for lower limbs working at an intensity of 60% 3RM (maximum weight that can be lifted three times with proper technique), results did not achieve statistical significant difference. The test used (STS 5 instead of STS 10) could explain the lack of significant results. Lord et al. (149) concluded that the STS 5 in community-dwelling older people depended on multiple sensimotor, balance and psychological processes, so it seems that STS 10 could be a more sensitive tool when measuring the effect of intradialytic resistance training interventions. The STS 10 as an indicator of quadriceps muscle strength (79) has been used in different patient population, such as polymyositis (142) and knee ostheorarthitis (150), but also in healthy elderly population (151).

5.c. Exercise Capacity

Exercise capacity of HD patients at baseline was found to be low, as measured by METs and time reached on the GXT. Deligiannis et al. (19) documented 40% higher time achieved on the GXT in healthy subjects compared with HD patients. Testing protocols varied within the literature, and so did results. While some authors using the modified Bruce protocol on the treadmill (19,34) achieved longer time, others using bike protocols (97) did not get such results. Mean exercise time in our study is in agreement with Moros et al. (97), where patients achieved almost 5 minutes using the Bruce protocol. Concerning METs, only Oh Park et al. (141) documented this parameter, and their results are slightly lower than ours, probably due to the inclusion of diabetic patients in a higher proportion than in our study. Muscular weakness and fatigue are the main limiting factor of exercise capacity (30,98,117). A wide variety of factors contribute to weakness in this cohort (115). By one side, sedentary behaviour of sleeping or watching TV predominates during HD treatment (more than 12 hours per week). By the other side, many potential contributors are present in HD patients, such as anaemia (43), malnutrition (37), peripheral neuropathy (11), hyperparathyroidism (53), carnitine deficiency (25), impaired blood flow to skeletal muscles (34) and muscle wasting (24). Peripheral dysfunction is found to limit more than other factors exercise capacity in HD patients (106).

After the 24-week intradialytic progressive resistance training program significant increases were found both in METs and exercise time. Similar improvement was observed after the completion of aerobic training programs (15,30,71,90,99,100,102,105,124-126,129,133) and also of combined programs including aerobic and resistance exercise training in HD (19,29,34,97) and predialysis patients (139). However, this is the first study examining the effects of intradialytic

resistance exercise training on exercise capacity. The improvements seen can partly be explained by the favourable skeletal muscle adaptations achieved by training (11,34,85,95-97). Sedentary behaviour has been associated with increased risk of death at 1 year (59). Additionally, exercise capacity measured by VO_2 peak is a powerful predictor of survival over 3,5-years follow-up (7). Therefore, the finding that our resistance exercise program on the HD chair enhances exercise capacity is of clinical importance aiming to improve survival.

The fact that hemoglobine showed a significant group per time interaction, with an increase on group B, supports previous findings concluding that exercise training is more important factor than increasing hematocrit to achieve higher exercise capacity (106).

5.d. Lower limb strength

In our study, quadriceps strength was measured by performing an isometric contraction. Only Cheema et al. (114) measured knee extension with an isometric dynamometer, but because the final result in their study was a combination of strength of three muscle groups, it is not comparable with the results in the present study. Comparison with other studies measuring strength is difficult due to the high variability of measurement tools and procedures used. Some studies used close bilateral chain or unilateral testing (29,34) while others used unilateral or bilateral 1RM or 3RM knee extension measurement (26,116,121,134,135,141). However, in predialysis patients knee extension strength was found to be low compared to healthy subjects (26,116).

At the end of our study a significant group per time interaction was found on the right knee extensor muscles strength (Group A increased by 6% and Group B decreased by 8 %) despite the highly inter-individual variability in response to training found in HD patients (92). Our results are in agreement with previous studies where also higher muscle strength on leg extensor muscles after resistance training was achieved (114,116,121) mainly in the participants' dominant leg (115,136). The improvement in muscle strength could partly be explained by the morphological adaptations of skeletal muscles to training. It is well established that a period of resistance training enhances protein synthesis in human skeletal muscles (152-155), which might be mediated by pre-translational, translational or post-translational events (153,154). The intradialytic resistance exercise programme seems to counteract the muscular atrophy associated with the sedentary behaviour of HD patients increasing their muscle strength, and thus may lead to a decrease in muscle fatigue and an improvement in everyday life activities (117).

5.e. Health Related Quality of Life

Concerning the quality of life indices at baseline the PCS of the SF-36 was found to be low in HD patients. Similar results were observed in previous studies (9,78,82,141) that found low PCS value with a variability of 12,6 points among them. Moreover, our patients showed lower values on the MCS than general population. This result is in agreement with the values observed in previous studies analysing HRQoL in this cohort (78,79,82,141), although the punctuation was slightly lower in our study.

Intradialytic training was not capable to affect statistically the HRQoL indices in our study. Several factors could explain the disagreement with previous studies that

showed significant improvement in PCS, that accounted by 0,4 (82), 3,2 (78) and 8,9 points (141). By one side, HD patients on Painter et al. (78) and Oh Park et al. (141) scored lower baseline values than our sample, which may cause the lack of significant change (131). Painter et al. (78) included a higher percentage of patients with Diabetes Mellitus compared to our study (43,7 vs 8% of patients), which could be responsible for the lower baseline level on PCS (9). By the other side, the study by Molsted et al. (82) included a bigger sample size than the present study, so the chance of falsely rejecting the null hypothesis decreased. The fact that this was the first time for intradialytic exercise training in Spain was an inhibitory factor for the less functional patients to voluntarily participate (156). As a result the sample size was small and higher functioning patients volunteered to participate. The fact that exercise was held in the Renal Unit during dialysis should be considered as an important factor affecting our results. On the contrary, an outpatient exercise program in group may influence positively and strongly the indices of HRQoL. Concerning the MCS, only an uncontrolled trial by Oh Park et al. (141) and a nonrandomized controlled trial by Segura et al. (137) found a significant increase of 6 and 8 points respectively, while previous RCTs found non significant increase (78,79) or decrease (82). The improvement found on both exercise groups in the present study could reflect the mental benefits of any kind of exercise participation reported in general population (147).

The slight improvement in the HRQoL indices after training in our patients, even if it is not statistically significant, should be viewed as an indeterminate, rather than a negative result. The study by López-Revuelta et al. (9) on relationship between HRQoL and morbidity and survival included more than 300 HD patients and found that MCS was the only variable associated with morbidity. Moreover, an increase of 5 points

on the PCS was found to be associated with a 10% increased survival (70). Therefore, the results of our study showing a tendency to increase both PCS and MCS support a potential impact on morbidity and mortality of any kind of exercise participation in HD patients.

It is beyond the scope of this thesis to investigate the effects of resistance exercise on haematological variables.

CHAPTER 6: CONCLUSIONS

1. Intradialytic resistance training results in statistical improvement in exercise capacity (METS achieved on the GXT).
2. Intradialytic resistance training results in statistical improvement in strength of knee extensor muscles at the dominant leg.
3. Intradialytic resistance training results in statistical improvement in physical functioning tests (6MWT: meters walked in 6 minutes; STS-10: time to perform 10 repetitions from sit to stand position; and STS-60: number of repetitions in 60 seconds).
4. Intradialytic resistance training results in clinical improvement in HRQoL, as measured by the SF-36.
5. Future studies should clarify if the inclusion of close chain exercises in a resistance training program is responsible for the increased benefits in performance of activities of daily living in HD patients.

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