Body composition and exercise intolerance in renal transplant patients: the response to exercise training

ISBN 10: 90-5278-562-7
ISBN 13: 978-90-5278-562-2

Cover design: 'In beweging' by Sjer Jacobs, Tegelen, 2006
Layout: Tiny Wouters
Production: Datawyse | Universitaire Pers Maastricht

The studies in this thesis were performed at the Nutrition and Toxicology Research Institute Maastricht (NUTRIM). The research described in this thesis was made possible by the 'Stichting ter bevordering van het wetenschappelijk onderwijs en onderzoek in de Interne Geneeskunde' and by a research grant of the Dutch Kidney Foundation (Nierstichting Nederland).

Printing of this thesis was financially supported by the Dutch Kidney Foundation, the Dutch Transplant Association (Nederlandse Transplantatie Vereniging, NTV), Astellas Europe B.V., Novartis Pharma B.V., Roche Nederland B.V. and Wyeth Pharmaceuticals B.V.

Body composition and exercise intolerance in renal transplant patients: the response to exercise training

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op donderdag 26 oktober 2006 om 14.00 uur

door

Eugénie Catharina Hubertina van den Ham

Promotores

Prof. dr. J.P. van Hooff
Prof. dr. ir. A.M.W.J. Schols
Prof. dr. K.M.L. Leunissen

Copromotor

Dr. J.P. Kooman

Beoordelingscommissie

Prof. dr. E.F.M. Wouters (voorzitter)
Prof. dr. J. Floege (University of Aachen, Aachen, Germany)
Prof. dr. H. Kuipers
Dr. P.L. Painter (University of California, San Francisco, USA)
Prof. dr. K.R. Westerterp

Voor Niki , Idy & Har

Contents

Chapter 1

General introduction and outline of the thesis

ECH van den Ham, JP Kooman, JP van Hooff
Partly published in: Nutritional considerations in renal transplant patients

Blood Purification 2002; 20:139-144

Introduction

The kidneys are complex organs performing a number of vital, life-sustaining functions. The main function of the kidneys is maintaining the milieu interior of the body within very narrow limits. This is achieved by regulating the acid-base and electrolyte state, excreting waste products of metabolism (uremic toxins) and removing excess body water. Furthermore, the kidneys secrete or activate hormones participating in the regulation of blood pressure, red blood cell production and calcium, phosphorus, and bone metabolism.
In patients with end-stage renal disease (ESRD), the function of the kidneys is impaired to such an extent that they are dependent upon renal replacement therapy for survival. There are two main types of renal replacement therapy: dialysis or renal transplantation. The incidence of renal replacement therapy for ESRD continues to increase throughout the world. Nowadays, diabetes mellitus, glomerulonephritis, and hypertension are the most important causes of ESRD[1,2]. In the Netherlands, the incidence rate of ESRD increased from 69.4 per million population in 1990 to 103.7 per million population in 2004 (data from the National Dutch Registry of Patients on Renal Replacement Therapy (RENINE), Rotterdam, The Netherlands[3]). In the beginning of the year 2005, 5259 patients were treated with dialysis, while 6292 patients were living with a functioning graft[3]. The number of ESRD patients is expected to further increase in the near future, because of aging and the increasing incidence of diabetes and cardiovascular disease.

Dialysis therapies, such as hemodialysis (HD) or peritoneal dialysis, can only partly correct the derangements in the milieu interior of ESRD patients. Dialysis patients may still suffer from uremic complications such as fluid overload, hypertension, anemia, disturbances in the calcium-phosphate metabolism, and insufficient removal of uremic toxins. Both HD and peritoneal dialysis patients have a greatly increased mortality risk compared to the general population. Five-year survival rates are reported to be between 34.7 and 60%[2,4-6].
The main cause of morbidity and mortality in dialysis patients is cardiovascular disease[2,7-9]. Both atherosclerosis and hypertension are highly prevalent in dialysis patients. Moreover, structural abnormalities of the heart and blood vessels, such as left ventricular hypertrophy and an increase in arterial rigidity, frequently occur.
Another factor strongly related to the high morbidity and mortality in dialysis patients is malnutrition[7,10-13]. Malnutrition is common in dialysis patients: 23-76% of the HD patients[14-20] and 18-56% of the peritoneal dialysis patients[20-22] are reported to be malnourished. The clinical features of malnutrition in dialysis patients may vary from a gradual loss of fat mass (FM) and lean body mass (LBM) due to a reduction in protein and energy intake, to a

complex picture including severe muscle wasting and a decline in plasma levels of serum albumin, transferrin, pre-albumin, and other visceral proteins[23,24]. Functional consequences of malnutrition are mainly caused by skeletal muscle wasting. Muscle wasting may be a significant contributor to limitations in physical functioning of dialysis patients[25]. Physical functioning and performance are markedly impaired in dialysis patients, resulting in a sedentary life-style and a severely reduced quality of life (QoL)[26].
Chronic inflammation, as reflected by elevated levels of serum C-reactive protein or proinflammatory cytokines, is another important risk factor for morbidity and mortality in dialysis patients[7,27-31]. Inflammation is a common feature of chronic renal failure. About 30-50% of the dialysis patients have serologic evidence of an activated inflammatory response[10,29-31].
In dialysis patients strong associations between inflammation, malnutrition, and atherosclerosis have been found[32]. This so called malnutrition-inflammation-atherosclerosis (MIA) syndrome is associated with an exceptionally high mortality rate[33].

A successful renal transplantation can reverse the uremic complications associated with ESRD. However, the renal function in renal transplant (RTx) patients often remains subnormal. Moreover, RTx patients are dependent upon immunosuppressive agents in order to prevent rejection of the transplanted kidney. These immunosuppressive agents - such as calcineurin inhibitors and steroids - are associated with a variety of side-effects, among others diabetes mellitus, gingival hyperplasia, hyperlipidemia, hypertension, osteoporosis, and weight gain[34,35]. Despite these relative drawbacks, the survival probability of RTx patients is significantly superior compared to dialysis patients on the waiting list for transplantation[36,37]: five-year survival rates are reported to be about 71 and 74% for recipients of cadaveric kidney transplants in Europe and The United States, respectively, and about 77 and 92% for living donor transplant patients[2,4]. Moreover, renal transplantation has important beneficial effects on the QoL[37-39]. It is also a cost-effective treatment option compared to dialysis[40-43]. Therefore, renal transplantation is the preferred treatment for patients with ESRD.

Several aspects of renal transplantation have not yet been widely investigated. Although nutritional status and physical performance have a great impact on the QoL of chronically ill patients, it is surprising that nutritional status and physical performance in RTx patients have received as little attention as it has. It is generally believed that nutritional status and physical performance improve after renal transplantation[44-46]. However, hardly any detailed information is present on alterations in body composition and physical performance and the determinants of these changes in RTx patients. The impact of renal

transplantation on body composition is likely to be complex and might be mediated by multiple factors such as the reversal of the uremic state, the use of immunosuppressive agents, intercurrent disease or rejection episodes, and changes in physical activity after renal transplantation.

Effects of the reversal of the uremic state in renal transplant patients

The effect of the uremic state on nutritional state and body composition is complex and multifactorial. In general, appetite is reduced in patients with end-stage renal failure. This might be due to an accumulation of appetite-suppressing factors in the mid-molecular range in the uremic plasma[47]. It has also been suggested that the elevated leptin levels in uremic patients might contribute to reduced appetite in this population[48]. Moreover, factors like metabolic acidosis, chronic inflammation and/or the resistance to anabolic hormones such as growth hormone, insulin, and insulin-like growth factor-I, may contribute to malnutrition in patients with ESRD[49]. These factors stimulate protein breakdown in muscle and activate a common proteolytic pathway, the ubiquitin-proteasome pathway[50]. In addition, acidosis and inflammation suppress hepatic albumin synthesis[51,52]. Furthermore, factors associated with the dialysis procedure itself - such as the loss of nutrients (glucose, amino acids, proteins, and vitamins) in the dialysate and dialysis membrane and fluid bio-incompatibility - may contribute to malnutrition in patients with ESRD[33,49].

A successful renal transplantation improves or reverses the uremic factors associated to malnutrition in dialysis patients. Appetite increases after renal transplantation[53]. Interestingly, the hyperleptinemia appears to improve[54], but does not completely normalize after renal transplantation[55]. On the other hand, levels of neuropeptide-Y, a strong appetite stimulant, were found to be significantly higher in RTx patients compared to dialysis patients[55]. The cause of the persistent hyperleptinemia in RTx patients is as yet unknown, but appears not to be related to graft function or immunosuppressive agents[55].

In general, body weight indeed seems to increase after renal transplantation. RTx patients are, however, at risk for excessive weight gain and centripetal obesity because of their long-term glucocorticoid requirements[56-60]. Moore et al.[56] found a mean weight gain of 4.0 kg during the first six months after renal transplantation in a group of patients which was treated with 0.5 mg steroids per kg ideal body weight (IBW) in the first three months after transplantation and with 0.2 mg steroids per kg IBW after the first three months. Merion et al.[57] found an average weight gain of 8.9 kg in non-obese patients and of 14.2 kg in obese patients during the first year after renal transplantation; both the obese and non-obese patients received immunosuppressive therapy with high

dosages of corticosteroids (more than 10 mg/day), cyclosporine and azathioprine. It has to be mentioned that the maintenance dosages of corticosteroids in the studies of Moore et al.[56] and Merion et al.[57] were relatively high in comparison with newer immunosuppressive strategies. Nowadays, RTx patients are receiving relatively low-dose corticosteroid maintenance therapy or even steroid-free maintenance therapy. Whether these low maintenance dosages of corticosteroids have comparable effects on the post-transplant body weight has, however, not been scrutinized.
The determinants of post-transplant changes in body weight have not been widely studied. Moreover, more research is needed to assess whether the post-transplant changes in body weight are due to an increase in LBM or an increase in body FM. Therefore, detailed data on body composition have to be obtained. Body composition data might provide insight into the relation with outcome, survival, and post-transplant complications; it might also affect approaches to nutritional therapy and to therapy in the field of physical activity. It is necessary to use precise and reliable methods to assess body composition in RTx patients accurately. However, only little is known about the validity of different techniques used to assess body composition in RTx patients.

Body composition in renal transplant patients

The weight gain after renal transplantation is not necessarily a negative finding. In many patients, post-transplant weight gain will just indicate improvement of their malnourished state. However, a point of concern raises when the post-transplant increase in body weight is due to an increase in body FM. In the few studies that have addressed the impact of renal transplantation on body composition, especially an increase in body FM was observed[61-65]. For example, Isiklar et al.[65] found a mean increase in body fat of 60% in 13 of the 15 studied patients within six months after renal transplantation, whereas LBM decreased in six of the 15 patients. A primary increase in body FM may have adverse effects on the lipid metabolism, glucose tolerance, and atherogenesis in RTx patients, which is especially important in view of the high cardiovascular morbidity and mortality in these patients[66-68]. Lipid abnormalities often observed in RTx patients are increased levels of very-low density lipoprotein (VLDL), low density lipoprotein (LDL) and total cholesterol, and hypertriglyceridemia[69]. Unfortunately, the influence of changes in body composition per se on these parameters of lipid metabolism is difficult to study in RTx patients, as many immunosuppressive drugs such as cyclosporine, rapamycin, and steroids also have adverse effects on the lipid profile. Although no study has directly assessed lipid parameters in relation to body composition in RTx patients, data from the general population have shown an increased risk of cardiovascular

disease, insulin resistance, and increased levels of triglycerides and reduced levels of high density lipoprotein cholesterol (HDL-cholesterol) in subjects with visceral obesity[70-72].
In the above mentioned studies which assessed changes in body composition after renal transplantation, patients were using relatively high doses of corticosteroids. Whether the use of relatively low maintenance doses of corticosteroids has comparable effects on body composition in RTx patients or not is less clear. In the present thesis, it is hypothesized that also low maintenance doses of corticosteroids can affect body composition.

Methods to assess body composition in renal transplant patients

Various techniques are available to measure body composition, among them isotope dilution, multi-frequency bio-electrical impedance analysis (MF-BIA), dual energy x-ray absorptiometry (DEXA), and anthropometry. In healthy individuals, isotope dilution techniques are considered the gold standard for measuring body water compartments. The dilution principle in its simplest form states that the volume of the water compartment is equal to the amount of tracer added to the compartment divided by the concentration of the tracer in that compartment[73]. Fat-free mass (FFM) can be derived from the total body water (TBW). For this, the body is supposed to be composed of two components: the FM and FFM. This two-component model is based on the knowledge that lipids are hydrophobic and thus free of water, which is therefore restricted to the fat-free compartment. The calculation of the FFM from the TBW depends on the assumption that the FFM contains a relatively constant proportion of water (73.2%)[74]. Disadvantages of the dilution techniques are the relatively complexity when used in the clinical practice, the need for advanced laboratory facilities, and the high costs.
MF-BIA is a relative inexpensive, non-invasive, easy to use, and portable technique, and therefore suitable for routine clinical use. MF-BIA is based on the different conductive and dielectric properties of various biological tissues at various frequencies of current. Blood, muscles, and other tissues which contain a lot of water and electrolytes are highly conductive. In contrast, bone, fat tissue, and air-filled spaces are highly resistive. Currents will flow predominantly through materials with higher conductivities[75]. MF-BIA measures body impedance at a wide range of frequencies. The advantage of MF-BIA above the classic single frequency bio-impedance measurements is the possibility of MF-BIA to discriminate between the extra-cellular and intracellular water compartment. At low frequencies, cell membranes act like a condenser and completely block the flow of the current through the intracellular pathway.

At higher frequencies, the condenser function of the cell membranes is lost and the current flows to both the extra- and intracellular compartments and thus to the TBW[76-78]. MF-BIA predicts the volume of the water compartments from a general mixture theory, assuming specific resistances for the extra- and intracellular water (ECW and ICW)[76,77,79,80]. FFM and FM are calculated from the thus derived ECW and ICW volume[77]. MF-BIA is considered a useful technique for body composition analysis in healthy individuals[81]. However, it is not known whether MF-BIA is also applicable for accurate body composition measurements in RTx patients.

The assessment of body composition in patients in which the hydration state may be disturbed, is difficult. None of the techniques available to measure body composition for routine clinical use can be viewed as gold standard. DEXA emits x-ray beams of different energy levels, which are attenuated differently by various body tissues. FM, LBM, and bone mineral content can be estimated directly from the attenuation ratios[82,83]. DEXA is considered to be superior to other non-invasive techniques for determining body composition in renal failure[84]. It has been widely applied for studies of body composition in dialysis and RTx patients[63,84,85]. It has, however, to be kept in mind that, although the state of hydration does not affect the estimate of FM with DEXA, it does affect that of LBM. A drawback of the DEXA method is that patients are exposed to (low doses of) radiation. Moreover, DEXA is more expensive and more complicated to perform than MF-BIA and anthropometry. Therefore, from a practical point of view, it might be advantageous if DEXA as a method to assess body composition could be replaced by MF-BIA or anthropometry.

Anthropometry measures skinfolds at the biceps, triceps, subscapula, and iliac crest with the use of a skinfold caliper. The sum of skinfolds can be used in the regression equations of Durnin and Womersly[86] to compute body density. FM and FFM can then be obtained from the body density and the body weight[86,87]. Skinfold thickness measurements are rapid, easy, noninvasive, and inexpensive, but strongly operator dependent and also not free of assumptions. It is assumed that the majority of body fat resides in subcutaneous regions, that there is a consistent relationship between subcutaneous and visceral fat, and that body fat distribution is stable[88-90]. Moreover, a constant hydration state of the FFM is assumed[89,91].

In dialysis patients, different methods to assess body composition have been compared. DEXA was more closely related to reference methods as neutron activation analysis, compared to MF-BIA and other techniques[84]. Also a disagreement between MF-BIA and isotope dilution techniques was observed, which was found to be related to the degree of overhydration[92]. Overhydration may impair the reliability of bio-impedance methods firstly because fluid accumulated in the trunk is not well measured by so-called “whole-body” bio-

impedance methods[75,93]. Secondly, abnormalities in fluid state may interfere with the reliability of constants used to calculate body water compartments[94,95]. In RTx patients, the assumption of a constant hydration status is not invariably true. Still, to the best of our knowledge, only one study compared different techniques (i.e., DEXA and anthropometry) to assess body composition in RTx patients[63]. Therefore, more research in this field is needed. In this thesis, MF-BIA is validated for its use in RTx patients. For this purpose, MF-BIA is compared to isotope dilution for the measurement of body water compartments. Furthermore, MF-BIA, DEXA, and anthropometry are compared to one another for measurement of the body fat and fat-free compartment.

Potential determinants of changes in body weight and body composition in renal transplant patients

Potential factors involved in the post-transplant changes in body weight and body composition in RTx recipients are 1) the use of immunosuppressive agents, in particular corticosteroids, 2) episodes of rejection and renal function, 3) dietary intake, and 4) physical activity level. These factors will be discussed below.

Immunosuppressive agents

Glucocorticoids are known to have profound effects on adipocytes, altering both lipid accumulation and mobilization. They usually cause weight gain and especially centripetal obesity (i.e., increased fat deposition in the peritoneum, mediastinum, and in subcutaneous sites on the face (moon-face) and the neck)[58,59,96]. Moreover, glucocorticoids are known to cause skeletal muscle wasting and weakness[97,98]. Steroid treatment might influence body composition by inducing changes in resting energy expenditure and substrate oxidation rates[64]. Steiger et al.[64] found a positive relation between protein and glucose oxidation, and an inverse relation between fat oxidation and daily steroid dose (0.1-0.5 mg/kg body weight) in RTx patients. The protein catabolic effects of high dose steroids already appear to be of importance in the first days after transplantation, as Hoy et al.[99] observed a significantly higher protein breakdown in RTx patients who were treated with high induction doses of corticosteroids (3-5 mg/kg/day) compared to patients who received 1 mg/kg/day as induction dose. The catabolic effects of glucocorticoid therapy thus appear to be dose dependent[64].

In contrast to high doses of corticosteroids, the influence of relatively low maintenance doses of steroids on body composition is uncertain. With regard to muscle mass, Horber et al.[97] and Miller et al.[44] found evidence of a reduced

muscle mass in RTx patients with a stable graft function on an average maintenance dose of 9.6 and 16.6 mg prednisone/day, respectively.
With regard to post-transplant weight gain, Johnson et al.[100] did not find a significant relationship between the cumulative steroid dose and post-transplant weight gain in the first year after renal transplantation. Also in two studies in heart transplant patients, no significant differences in weight gain between patients receiving prednisolone therapy and patients tapered off prednisolone therapy were found[101,102]. In contrast, Hagan et al.[103] found that successful withdrawal of corticosteroids in the first year after heart transplantation decreased post-transplant weight gain.
In summary, the effects of high maintenance doses of corticosteroids on body composition are well established. However, the effects of low maintenance doses of steroids on body composition have to be elucidated. In the present thesis, the influence of relatively low maintenance doses of corticosteroids on body composition is studied. It is hypothesized that also low-dose corticosteroid treatment affects body composition.

Episodes of rejection and renal function

In the early post-transplant period, many changes occur which can be of influence on body weight and body composition, such as loss of excess ECW due to improvement of the renal function. On the other hand, the surgical procedure, intercurrent infections or acute rejection episodes may lead to a further decline in LBM. Steiger et al.[64] found a tendency towards a decline in LBM between day 11 and 42 after renal transplantation, after which it tended to increase. Acute rejection episodes indeed appear to have an effect on changes in body composition in the first months after transplantation, as the occurrence of rejection periods in patients who lost body weight in the first six months after renal transplantation was significantly higher compared to patients who gained weight during this period[56]. This is probably at least partly related to the protein catabolic effects of high dose corticosteroids, which are often used to treat acute rejection episodes[99]. Moreover, factors accompanying rejection episodes, such as (prolonged) hospitalization, increased stress, complications (e.g., infections), prolonged effects of uremia, catabolism, feeling of malaise or decreased appetite, might be involved. However, the long-term effect of acute rejection episodes on body weight after renal transplantation is not widely studied. In the single study which addressed this topic, Johnson et al.[100] did not find a relation between weight gain five years after transplantation and rejection history.
It should be stressed that also after a successful renal transplantation, the renal function often remains subnormal or becomes disturbed in a later stage. Among others, this is due to the quality of the donor kidney and to the

occurrence of acute rejection and/or chronic allograft nephropathy (CAN). Studies in non-transplanted patients with chronic renal failure show a gradual deterioration of food intake and nutritional status which is related to the degree of renal dysfunction[104]. In RTx patients, the influence of a suboptimal renal function on nutritional state has not been widely investigated, although Johnson et al.[100] did not find a relation between weight gain during the first five years after renal transplantation and post-transplant renal function.

Dietary intake

Another factor that may contribute to post-transplant changes in body weight and body composition is the nutrient intake of the RTx patients. After renal transplantation, the feeling of well-being, the disappearance of dietary restrictions, and also the increased appetite, may result into an increased nutrient intake. A chronic increase of energy intake without an increase of energy expenditure will lead to weight gain. The relation between dietary intake and body composition is, however, difficult to study, because of the variations in dietary intake within individual patients and the relative unreliability of dietary assessments[105].

In the immediate post-transplant period, patients are often hypercatabolic and are invariably in negative nitrogen balance when protein intake is below 1 g/kg/day of protein[99]. Whittier et al.[106] showed that in patients receiving high doses of steroids in the immediate post-transplant period as much as 1.3-1.5 g/kg/day protein intake is needed to prevent protein breakdown. A caloric intake of 30-35 kcal/kg/day is currently advised in this setting[107].

In general, dietary recommendations in stable RTx patients do not differ from those in the general population[108]. Fat intake should be below 30% of total energy intake and should include a polysaturated to saturated fat ratio of more than 1. In patients with a stable renal function, protein intake should be approximately 1 g/kg body weight[107]. In patients with chronic transplant nephropathy, a moderately low protein diet (0.55-0.80 g/kg body weight) was found to reduce proteinuria and to stabilize renal function[109,110], although this topic will need to be addressed in randomized studies with close attention for the nutritional aspects of such a diet. With regard to other nutrients, calcium intake should in general be liberal (>1200 mg/day), and calcium supplementation may be needed as a preventive strategy for post-transplant osteoporosis. In RTx patients on tacrolimus- or cyclosporine-based immunosuppression, magnesium intake merits special attention[111,112]. Oral phosphorus supplementation is essential in patients with severe hypophosphatemia (serum phosphate levels <0.30 mmol/l), but is also indicated in patients with mild hypophosphatemia (serum phosphate levels between 0.30 and 0.75 mmol/l)[113]. Especially in hypertensive patients, sodium

intake should be restricted (±2000 mg/day). Intensive dietary counseling is indicated in patients with excessive post-transplant weight gain and hyperlipidemia; next to dietary restrictions, statin therapy is widely used in the management of post-renal transplantation hyperlipidemia[114,115].

Physical activity level

Physical activity may also have an influence on body composition. Physical activity plays a major role in preventing weight gain[116,117]. In general, by increasing the physical activity level, FFM will increase and FM will decrease[117-120]. In addition, in subjects who exercise regularly, less adipose tissue appears to accumulate in the upper, central body regions as they get older[121].

Regular physical activity has beneficial effects on health and disease. It decreases the risk of overall and cardiovascular disease mortality, the latter by improving cardiovascular risk factors such as blood pressure and lipid profile[122-125]. Furthermore, regular physical activity plays an important role in the prevention and treatment of obesity and non-insulin dependent diabetes mellitus[122,126]. Moreover, benefits on the musculoskeletal system, mental health and health-related QoL are described[122]. Regular physical activity thus has important positive effects on medical problems highly prevalent in renal patients. In particular the effects on cardiovascular risk factors are of great potential importance given the high incidence of cardiovascular morbidity and mortality in renal patients[127].

The levels of physical activity are low both in HD and RTx patients[128-130]. In healthy subjects, physical activity level has been proven to be significantly, positively related to physical fitness, i.e., exercise capacity and muscle strength[131,132]. Physical fitness is an important determinant of physical functioning and performance[133]. Limitations in physical functioning and performance adversely affect QoL.

Surprisingly, in RTx patients only few data are present on the relation between physical activity and body composition. Also the relation between physical activity level and physical performance has not been widely investigated in RTx patients. Moreover, potential determinants of exercise capacity in RTx patients have to be elucidated.

Exercise capacity in renal transplant patients

Exercise intolerance is common in patients with ESRD receiving chronic hemodialysis, and severely compromises QoL. Although exercise capacity

appears to improve spontaneously after renal transplantation, it often remains subnormal[45,46].

Potential factors influencing exercise capacity in HD patients are factors related to the uremic state or the dialysis treatment itself, skeletal muscle wasting and weakness, and physical inactivity. Successful transplantation corrects or improves many of the systemic abnormalities influencing exercise capacity in HD patients. However, the use of corticosteroids, the often subnormal renal function, and physical inactivity, may still lead to abnormalities in body composition in RTx patients, and in particular to a decreased muscle mass. Skeletal muscle weakness and fatigue appear to be the most important factors limiting the maximum exercise tolerance, both in patients who have undergone renal transplantation and in HD patients[45,134]. In the present thesis, it is hypothesized that the severity of muscle weakness and exercise intolerance is less in RTx patients compared to HD patients, in whom factors such as chronic inflammation, acidosis, and malnutrition may have detrimental effects on physical performance, but worse compared to healthy controls. Moreover, it is hypothesized that physical inactivity and possibly the use of steroids and a subnormal renal function are important determinants of muscle weakness and exercise intolerance in RTx patients.

Exercise training appears to improve exercise capacity, skeletal muscle strength, and QoL in RTx patients[45,135,136]. In HD patients, beneficial effects of training were also observed[137-143]. However, it is not known whether the response to training in RTx patients is comparable to the response in healthy individuals, because of the use of corticosteroids and the often subnormal renal function in RTx patients. Moreover, the response to training may even be lower in HD patients, due to the presence of multiple catabolic factors related to the uremic state, such as metabolic acidosis, malnutrition, and inflammation. In this thesis, it is hypothesized that exercise capacity, muscle strength, and QoL improve after exercise training in RTx and HD patients, and that the functional response in RTx patients is less compared to healthy controls and higher compared to HD patients.

Outline of the thesis

The research described in this thesis addresses the following aspects:

1. the changes in body weight after renal transplantation and the potential determinants of these changes;
2. the assessment of techniques for accurate body composition measurements in RTx patients and the evaluation of post-transplant changes in body composition as well as the potential determinants of these changes;

3. the physical performance of RTx and HD patients as well as the potential determinants of impaired physical functioning and performance in RTx patients;
4. the effects of intensive, supervised exercise training on exercise capacity, skeletal muscle strength, body composition, and QoL in RTx and HD patients.

In the study described in **chapter 2,** the changes in body weight after renal transplantation were investigated. Moreover, the relationship between potential factors affecting body weight and post-transplant changes in body weight -such as corticosteroid dose, age, gender, pre-transplant body mass index and dialysis modality, occurrence and treatment of rejection, and post-transplant renal function- was elucidated in that chapter.
In **chapter 3**, MF-BIA was validated for its use in RTx patients by comparing MF-BIA to isotope dilution for measurement of the body water compartments, and by comparing MF-BIA, DEXA, and anthropometry to one another for measurement of the body fat and fat-free compartment. In **chapter 4,** the results of a prospective study towards the changes in body composition in the early post-transplant period were reported. In **chapter 5,** the effects of early steroid withdrawal on body composition were studied in RTx patients in the early post-transplant period. In **chapter 6**, the relation between corticosteroid dose, physical activity and dietary intake, and body composition was investigated in a group of stable RTx patients.
In the study described in **chapter 7**, it was assessed to what extent exercise capacity and skeletal muscle strength of RTx patients differ from HD patients and healthy controls. Moreover, potential determinants of exercise capacity and skeletal muscle strength in RTx patients were elucidated. In **chapter 8**, the effects of intensive, supervised exercise training on exercise capacity, skeletal muscle strength, body composition, and QoL were assessed and compared in RTx patients, HD patients and healthy controls.
In **chapter 9**, a summary of the main findings of this thesis is given. These findings are discussed in the context of the recent literature. Moreover, the conclusions of the thesis are presented in this chapter.

References

1. Stengel B, Billon S, Van Dijk PC, Jager KJ, Dekker FW, Simpson K, Briggs JD. Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990-1999. Nephrol Dial Transplant 2003; 18(9):1824-1833.
2. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US Renal Data System. The 2005 USRDS Annual Data Report: Atlas of End-Stage Renal Disease in The United States. 2005.
3. National Dutch Registry of Patients on Renal Replacement Therapy (RENINE), 2005.
4. ERA-EDTA Registry. ERA-EDTA Registry 2003 Annual Report, 2005.
5. Maiorca R, Cancarini GC, Zubani R, Camerini C, Manili L, Brunori G, Movilli E. CAPD viability: a long-term comparison with hemodialysis. Perit Dial Int 1996; 16(3):276-287.
6. Schaubel D, Desmeules M, Mao Y, Jeffery J, Fenton S. Survival experience among elderly end-stage renal disease patients. A controlled comparison of transplantation and dialysis. Transplantation 1995; 60(12):1389-1394.
7. Qureshi AR, Alvestrand A, Divino-Filho JC, Gutierrez A, Heimburger O, Lindholm B, Bergstrom J. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol 2002; 13(Suppl 1):S28-36.
8. Foley RN, Parfrey PS. Cardiovascular disease and mortality in ESRD. J Nephrol 1998; 11(5):239-245.
9. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephrol 1999; 10(7):1606-1615.
10. Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, Bergstrom J. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. Kidney Int 1998; 53(3):773-782.
11. Marckmann P. Nutritional status and mortality of patients in regular dialysis therapy. J Intern Med 1989; 226(6):429-432.
12. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. J Am Soc Nephrol 1996; 7(5):728-736.
13. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ. Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 1998; 31(6):997-1006.
14. Young GA, Swanepoel CR, Croft MR, Hobson SM, Parsons FM. Anthropometry and plasma valine, amino acids, and proteins in the nutritional assessment of hemodialysis patients. Kidney Int 1982; 21(3):492-499.
15. Schoenfeld PY, Henry RR, Laird NM, Roxe DM. Assessment of nutritional status of the National Cooperative Dialysis Study population. Kidney Int Suppl 1983; 13:S80-88.
16. Guarnieri G, Toigo G, Situlin R, Faccini L, Coli U, Landini S, Bazzato G, Dardi F, Campanacci L. Muscle biopsy studies in chronically uremic patients: evidence for malnutrition. Kidney Int Suppl 1983; 16:S187-193.
17. Marckmann P. Nutritional status of patients on hemodialysis and peritoneal dialysis. Clin Nephrol 1988; 29(2):75-78.
18. Enia G, Sicuso C, Alati G, Zoccali C. Subjective global assessment of nutrition in dialysis patients. Nephrol Dial Transplant 1993; 8(10):1094-1098.
19. Lowrie EG. Chronic dialysis treatment: clinical outcome and related processes of care. Am J Kidney Dis 1994; 24(2):255-266.
20. Cianciaruso B, Brunori G, Kopple JD, Traverso G, Panarello G, Enia G, Stippoli P, De Vacchi A, Querques M, Viglino G. Cross-sectional comparison of malnutrition in continuous ambulatory peritoneal dialysis and hemodialysis patients. Am J Kidney Dis 1995; 26(3): 475-486.
21. Bergstrom J, Lindholm B. Nutrition and adequacy of dialysis. How do hemodialysis and CAPD compare? Kidney Int Suppl 1993; 40:S39-50.

22. Young GA, Kopple JD, Lindholm B, Vonesh EF, De Vecchi A, Scalamogna A, Castelnova C, Oreopoulos DG, Anderson GH, Bergstrom J. Nutritional assessment of continuous ambulatory peritoneal dialysis patients: an international study. Am J Kidney Dis 1991; 17(4):462-471.
23. Locatelli F, Fouque D, Heimburger O, Drueke TB, Cannata-Andia JB, Horl WH, Ritz E. Nutritional status in dialysis patients: a European consensus. Nephrol Dial Transplant 2002; 17(4):563-572.
24. Stenvinkel P. Malnutrition and chronic inflammation as risk factors for cardiovascular disease in chronic renal failure. Blood Purif 2001; 19(2):143-151.
25. Krasnoff J, Painter P. The physiological consequences of bed rest and inactivity. Adv Ren Replace Ther 1999; 6(2):124-132.
26. Johansen KL. Exercise and chronic kidney disease: current recommendations. Sports Med 2005; 35(6):485-499.
27. Bologa RM, Levine DM, Parker TS, Cheigh JS, Serur D, Stenzel KH, Rubin AL. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis 1998; 32(1):107-114.
28. Kimmel PL, Phillips TM, Simmens SJ, Peterson RA, Weihs KL, Alleyne S, Cruz I, Yanovski JA, Veis JH. Immunologic function and survival in hemodialysis patients. Kidney Int 1998; 54(1):236-244.
29. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. Kidney Int 1998; 54(2):627-636.
30. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35(3):469-476.
31. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999; 55(2):648-658.
32. Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA, Bergstrom J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant 2000; 15(7): 953-960.
33. Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome - the heart of the matter. Nephrol Dial Transplant 2002; 17 (Suppl 11):S28-31.
34. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. Drugs 2000; 59(2):323-389.
35. Langone AJ, Harold Helderman J. Immunosuppression, in Medical Management of Kidney Transplantation. Weir MR, Editor. Lippincott Williams & Wilkins, Philadelphia. 2005:127-137.
36. Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol 1998; 9(11): 2135-2141.
37. McDonald SP, Russ GR. Survival of recipients of cadaveric kidney transplants compared with those receiving dialysis treatment in Australia and New Zealand, 1991-2001. Nephrol Dial Transplant 2002; 17(12):2212-2219.
38. Overbeck I, Bartels M, Decker O, Harms J, Hauss J, Fangmann J. Changes in quality of life after renal transplantation. Transplant Proc 2005; 37(3):1618-1621.
39. Fujisawa M, Ichikawa Y, Yoshiya K, Isotani S, Higuchi A, Nagano S, Arakawa S, Hamami G, Matsumoto O, Kamidono S. Assessment of health-related quality of life in renal transplant and hemodialysis patients using the SF-36 health survey. Urology 2000; 56(2):201-206.
40. de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. Health Policy 1998; 44(3):215-232.
41. Health Council of the Netherlands. Advice on dialysis and renal transplantation (in Dutch). 1986.
42. Croxson BE, Ashton T. A cost effectiveness analysis of the treatment of end stage renal failure. N Z Med J 1990; 103(888):171-174.

43. Ludbrook A. A cost-effectiveness analysis of the treatment of chronic renal failure. Applied Economics 1981; 13:337-350.
44. Miller DG, Levine SE, D'Elia JA, Bistrian BR. Nutritional status of diabetic and nondiabetic patients after renal transplantation. Am J Clin Nutr 1986; 44(1):66-69.
45. Kempeneers G, Noakes TD, van Zyl-Smit R, Myburgh KH, Lambert M, Adams B, Wiggins T. Skeletal muscle limits the exercise tolerance of renal transplant recipients: effects of a graded exercise training program. Am J Kidney Dis 1990; 16(1):57-65.
46. Painter P, Hanson P, Messer-Rehak D, Zimmerman SW, Glass NR. Exercise tolerance changes following renal transplantation. Am J Kidney Dis 1987; 10(6):452-456.
47. Anderstam B, Mamoun AH, Sodersten P, Bergstrom J. Middle-sized molecule fractions isolated from uremic ultrafiltrate and normal urine inhibit ingestive behavior in the rat. J Am Soc Nephrol 1996; 7(11):2453-2460.
48. Stenvinkel P. Leptin-a new hormone of definite interest for the nephrologist. Nephrol Dial Transplant 1998; 13(5):1099-1101.
49. Laville M, Fouque D. Nutritional aspects in hemodialysis. Kidney Int Suppl 2000; 76: S133-139.
50. Mitch WE. Insights into the abnormalities of chronic renal disease attributed to malnutrition. J Am Soc Nephrol 2002; 13(Suppl 1):S22-27.
51. Ballmer PE, McNurlan MA, Hulter HN, Anderson SE, Garlick PJ, Krapf R. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. J Clin Invest 1995; 95(1):39-45.
52. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. Semin Dial 2004; 17(6):432-437.
53. Hylander B, Barkeling B, Rossner S. Changes in patients' eating behavior: in the uremic state, on continuous ambulatory peritoneal dialysis treatment, and after transplantation. Am J Kidney Dis 1997; 29(5):691-698.
54. Landt M, Brennan DC, Parvin CA, Flavin KS, Dagogo-Jack S, Coyne DW. Hyperleptinaemia of end-stage renal disease is corrected by renal transplantation. Nephrol Dial Transplant 1998; 13(9):2271-2275.
55. Kokot F, Adamczak M, Wiecedilcek A, Spiechowicz U, Mesjasz J. Plasma immunoreactive leptin and neuropeptide Y levels in kidney transplant patients. Am J Nephrol 1999; 19(1): 28-33.
56. Moore LW, Gaber OA. Patterns of early weight change after renal transplantation. J Ren Nutr 1996; 6(1):21-25.
57. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, Rocher LL, Campbell DA. Obesity and renal transplantation. Surg Gynecol Obstet 1991; 172(5):367-376.
58. Yanovski JA, Cutler GB, Jr. Glucocorticoid action and the clinical features of Cushing's syndrome. Endocrinol Metab Clin North Am 1994; 23(3):487-509.
59. Danovitch GM. Immunosuppressive medications and protocols for kidney transplantation, in Handbook of kidney transplantation. Danovitch GM, Editor. Little Brown and Compagny, Boston. 1992:67-104.
60. Horber FF, Zurcher RM, Herren H, Crivelli MA, Robotti G, Frey FJ. Altered body fat distribution in patients with glucocorticoid treatment and in patients on long-term dialysis. Am J Clin Nutr 1986; 43(5):758-769.
61. Verran D, Munn S, Collins J, Hill G. Impact of renal allograft implantation and immunosuppression on body composition using in vivo neutron activation analysis. Transplant Proc 1992; 24(1):173-174.
62. Martin M, Lopes IM, Errasti P, Martinez JA. Body composition and biochemical profile as affected by diet and renal transplantation among renal patients. J Physiol Biochem 1998; 54(1):53-54.
63. Hart PD, Wilkie ME, Edwards A, Cunningham J. Dual energy X-ray absorptiometry versus skinfold measurements in the assessment of total body fat in renal transplant recipients. Eur J Clin Nutr 1993; 47(5):347-352.
64. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger P, Horber FF. Body composition and fuel metabolism after kidney grafting. Eur J Clin Invest 1995; 25(11):809-816.

65. Isiklar I, Akin O, Demirag A, Niron EA. Effects of renal transplantation on body composition. Transplant Proc 1998; 30(3):831-832.
66. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7(1):158-165.
67. Massy ZA, Kasiske BL. Post-transplant hyperlipidemia: mechanisms and management. J Am Soc Nephrol 1996; 7(7):971-977.
68. Wanner C, Quaschning T, Weingarnter K. Impact of dyslipidaemia in renal transplant recipients. Curr Opin Urol 2000; 10(2):77-80.
69. Pirsch JD, D'Alessandro AM, Sollinger HW, Knechtle SJ, Reed A, Kalayoglu M, Belzer FO. Hyperlipidemia and transplantation: etiologic factors and therapy. J Am Soc Nephrol 1992; 2(Suppl 12):S238-242.
70. DiPietro L, Katz LD, Nadel ER. Excess abdominal adiposity remains correlated with altered lipid concentrations in healthy older women. Int J Obes Relat Metab Disord 1999; 23(4): 432-436.
71. Albu JB, Kovera AJ, Johnson JA. Fat distribution and health in obesity. Ann N Y Acad Sci 2000; 904:491-501.
72. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. BMJ 1984; 288:1401-1404.
73. Edelman IS, Olney JM, James AH, Brooks L, Moore FD. Body composition: Studies in the human being by the dilution principle. Science 1952; 115:447-454.
74. Pace N, Rathbun EN. Studies on body composition III. The body water and chemically combined nitrogen content in relation to fat content. J Biol Chem 1945; 158:658-691.
75. Baumgartner RN. Electrical impedance and total body electrical conductivity, in Human Body Composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign, IL. 1996:79-107.
76. Van Loan MD, Kopp LE, King JC, Wong WW, Mayclin PL. Fluid changes during pregnancy: use of bioimpedance spectroscopy. J Appl Physiol 1995; 78(3):1037-1042.
77. De Lorenzo A, Andreoli A, Matthie J, Withers P. Predicting body cell mass with bioimpedance by using theoretical methods: a technological review. J Appl Physiol 1997; 82(5):1542-1558.
78. Kushner RF. Bioelectrical impedance analysis: a review of principles and applications. J Am Coll Nutr 1992; 11(2):199-209.
79. Hanai T. Electrical properties of emulsions, in Emulsion Science. Sherman PH, Editor. Academic Press, London. 1968:354-377.
80. Matthie J, Zarowitz B, De Lorenzo A, Andreoli A, Katzarski K, Pan G, Withers P. Analytic assessment of the various bioimpedance methods used to estimate body water. J Appl Physiol 1998; 84(5):1801-1816.
81. National Institute of Health. Bioelectrical impedance analysis in body composition measurement. National institutes of Health Technology Assessment Conference Statement. Am J Clin Nutr 1996; 64(Suppl 3):S524-532.
82. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990; 51(6): 1106-1112.
83. Lohman TG. Dual energy x-ray absorptiometry, in Human body composition. Roche AF, Heimsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:63-78.
84. Kerr PG, Strauss BJ, Atkins RC. Assessment of the nutritional state of dialysis patients. Blood Purif 1996; 14(5):382-387.
85. Heimburger O, Qureshi AR, Blaner WS, Berglund L, Stenvinkel P. Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. Am J Kidney Dis 2000; 36(6):1213-1225.
86. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 1974; 32(1):77-97.
87. Siri WE. The gross composition of the body. Adv Biol Med Phys 1956; 4:239-280.

88. Lukaski HC. Methods for the assessment of human body composition: traditional and new. Am J Clin Nutr 1987; 46(4):537-556.
89. Roche AF. Anthropometry and ultrasound, in Human Body Composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign, IL. 1996:167-190.
90. Jensen MD. Research techniques for body composition assessment. J Am Diet Assoc 1992; 92(4):454-460.
91. Going SB. Densitometry, in Human Body Composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign, IL. 1996:3-24.
92. Cox-Reijven PL, Kooman JP, Soeters PB, van der Sande FM, Leunissen KM. Role of bioimpedance spectroscopy in assessment of body water compartments in hemodialysis patients. Am J Kidney Dis 2001; 38(4):832-838.
93. Van Loan MD, Withers P, Matthie J, Mayclin PL. Use of bio-impedance spectroscopy (BIS) to determine extracellular fluid (ECF), intracellular fluid (ICF), total body water (TBW) and fat free mass (FFM), in Human Body Composition: In Vivo Methods, Models and Assessment. Ellis KJ, Eastman JD, Editors. Plenum, New York. 1993:67-70.
94. Di Iorio BR, Terracciano V, Bellizzi V. Bioelectrical impedance measurement: errors and artifacts. J Ren Nutr 1999; 9(4):192-197.
95. Ward LC, Elia M, Cornish BH. Potential errors in the application of mixture theory to multifrequency bioelectrical impedance analysis. Physiol Meas 1998; 19(1):53-60.
96. Peeke PM, Chrousos GP. Hypercortisolism and obesity. Ann N Y Acad Sci 1995; 771: 665-676.
97. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Evidence that prednisone-induced myopathy is reversed by physical training. J Clin Endocrinol Metab 1985; 61(1):83-88.
98. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Thigh muscle mass and function in patients treated with glucocorticoids. Eur J Clin Invest 1985; 15(6):302-307.
99. Hoy WE, Sargent JA, Freeman RB, Pabico RC, McKenna BA, Sterling WA, Jr. The influence of glucocorticoid dose on protein catabolism after renal transplantation. Am J Med Sci 1986; 291(4):241-247.
100. Johnson CP, Gallagher-Lepak S, Zhu YR, Porth C, Kelber S, Roza AM, Adams MB. Factors influencing weight gain after renal transplantation. Transplantation 1993; 56(4):822-827.
101. Lake KD, Reutzel TJ, Pritzker MR, Jorgensen CR, Emery RW. The impact of steroid withdrawal on the development of lipid abnormalities and obesity in heart transplant recipients. J Heart Lung Transplant 1993; 12(4):580-590.
102. Olivari MT, Jessen ME, Baldwin BJ, Horn VP, Yancy CW, Ring WS, Rosenblatt RL. Triple-drug immunosuppression with steroid discontinuation by six months after heart transplantation. J Heart Lung Transplant 1995; 14:127-135.
103. Hagan ME, Holland CS, Herrick CM, Rasmussen LG. Amelioration of weight gain after heart transplantation by corticosteroid-free maintenance immunosuppression. UTAH Cardiac Transplant Program. J Heart Transplant 1990; 9(4):382-384.
104. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int 2000; 57(4):1688-1703.
105. Kloppenburg WD, Stegeman CA, Hooyschuur M, van der Ven J, de Jong PE, Huisman RM. Assessing dialysis adequacy and dietary intake in the individual hemodialysis patient. Kidney Int 1999; 55(5):1961-1969.
106. Whittier FC, Evans DH, Dutton S, Ross G, Jr, Luger A, Nolph KD, Bauer JH, Brooks CS, Moore H. Nutrition in renal transplantation. Am J Kidney Dis 1985; 6(6):405-411.
107. Pruchno CJ, Hunsicker LG. Nutritional requirements of renal transplant patients, in Nutrition and the kidney. Mitch WE, Klahr S, Editors. Little Brown, Boston, 1993.
108. Edwards MS, Doster S. Renal transplant diet recommendations: results of a survey of renal dietitians in the United States. J Am Diet Assoc 1990; 90(6):843-846.
109. Bernardi A, Biasia F, Piva M, Poluzzi P, Senesi G, Scaramuzzo P, Garizzo O, Stoppa F, Cavallaro B, Bassini S, Bucciante G. Dietary protein intake and nutritional status in patients with renal transplant. Clin Nephrol 2000; 53(4):S3-5.

110. Salahudeen AK, Hostetter TH, Raatz SK, Rosenberg ME. Effects of dietary protein in patients with chronic renal transplant rejection. Kidney Int 1992; 41(1):183-190.
111. Lote CJ, Thewles A, Wood JA, Zafar T. The hypomagnesaemic action of FK506: urinary excretion of magnesium and calcium and the role of parathyroid hormone. Clin Sci (Lond) 2000; 99(4):285-292.
112. Frost L, Danielsen H, Dorup I, Kjaer T, Pedersen EB. Skeletal muscle magnesium content during cyclosporin and azathioprine treatment in renal transplant recipients. Nephrol Dial Transplant 1993; 8(1):79-83.
113. Ambuhl PM, Meier D, Wolf B, Dydak U, Boesiger P, Binswanger U. Metabolic aspects of phosphate replacement therapy for hypophosphatemia after renal transplantation: impact on muscular phosphate content, mineral metabolism, and acid/base homeostasis. Am J Kidney Dis 1999; 34(5):875-883.
114. Fellstrom B. Impact and management of hyperlipidemia posttransplantation. Transplantation 2000; 70(Suppl 11):S51-57.
115. Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. Transplantation 1997; 63(3):331-338.
116. Prentice AM, Jebb SA. Obesity in Britain: gluttony or sloth? BMJ 1995; 311(7002):437-439.
117. Wilmore JH. Increasing physical activity: alterations in body mass and composition. Am J Clin Nutr 1996; 63(Suppl 3):S456-460.
118. Epstein LH, Wing RR. Aerobic exercise and weight. Addict Behav 1980; 5(4):371-388.
119. Wilmore JH. Body composition in sport and exercise: directions for future research. Med Sci Sports Exerc 1983; 15(1):21-31.
120. Ballor DL, Keesey RE. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. Int J Obes 1991; 15(11): 717-726.
121. Kohrt WM, Malley MT, Dalsky GP, Holloszy JO. Body composition of healthy sedentary and trained, young and older men and women. Med Sci Sports Exerc 1992; 24(7):832-837.
122. Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention. JAMA 1996; 276(7):522.
123. Anderson JE, Boivin MR, Jr, Hatchett L. Effect of exercise training on interdialytic ambulatory and treatment-related blood pressure in hemodialysis patients. Ren Fail 2004; 26(5):539-544.
124. Stewart KJ, Bacher AC, Turner KL, Fleg JL, Hees PS, Shapiro EP, Tayback M, Ouyang P. Effect of exercise on blood pressure in older persons: a randomized controlled trial. Arch Intern Med 2005; 165(7):756-762.
125. Harter HR, Goldberg AP. Endurance exercise training. An effective therapeutic modality for hemodialysis patients. Med Clin North Am 1985; 69(1):159-175.
126. Watts K, Jones TW, Davis EA, Green D. Exercise training in obese children and adolescents: current concepts. Sports Med 2005; 35(5):375-392.
127. Fellstrom B, Jardine AG, Soveri I, Cole E, Gronhagen-Riska C, Neumayer HH, Maes B, Gimpelewicz C, Holdaas H. Renal dysfunction as a risk factor for mortality and cardiovascular disease in renal transplantation: experience from the Assessment of Lescol in Renal Transplantation trial. Transplantation 2005; 79(9):1160-1163.
128. Johansen KL, Chertow GM, Ng AV, Mulligan K, Carey S, Schoenfeld PY, Kent-Braun JA. Physical activity levels in patients on hemodialysis and healthy sedentary controls. Kidney Int 2000; 57(6):2564-2570.
129. Gallagher-Lepak S. Functional capacity and activity level before and after renal transplantation. Anna J 1991; 18(4):378-382.
130. Nielens H, Lejeune TM, Lalaoui A, Squifflet JP, Pirson Y, Goffin E. Increase of physical activity level after successful renal transplantation: a 5 year follow-up study. Nephrol Dial Transplant 2001; 16(1):134-140.
131. Wasserman K Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Third edition. Lippincott Williams and Wilkins, Baltimore, 1999.
132. Huang Y, Macera CA, Blair SN, Brill PA, Kohl HW, Kronenfeld JJ. Physical fitness, physical activity, and functional limitation in adults aged 40 and older. Med Sci Sports Exerc 1998; 30(9):1430-1435.

133. Painter P, Stewart AL, Carey S. Physical functioning: definitions, measurement, and expectations. Adv Ren Replace Ther 1999; 6(2):110-123.
134. Diesel W, Noakes TD, Swanepoel C, Lambert M. Isokinetic muscle strength predicts maximum exercise tolerance in renal patients on chronic hemodialysis. Am J Kidney Dis 1990; 16(2):109-114.
135. Miller TD, Squires RW, Gau GT, Ilstrup DM, Frohnert PP, Sterioff S. Graded exercise testing and training after renal transplantation: a preliminary study. Mayo Clin Proc 1987; 62(9): 773-777.
136. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL. A randomized trial of exercise training after renal transplantation. Transplantation 2002; 74(1):42-48.
137. Painter PL, Nelson-Worel JN, Hill MM, Thornbery DR, Shelp WR, Harrington AR, Weinstein AB. Effects of exercise training during hemodialysis. Nephron 1986; 43(2):87-92.
138. Koufaki P, Mercer TH, Naish PF. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. Clin Physiol Funct Imaging 2002; 22(2): 115-124.
139. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Tourkantonis A, Deligiannis A. The effects of exercise training on muscle atrophy in haemodialysis patients. Nephrol Dial Transplant 1998; 13(3):685-699.
140. Headley S, Germain M, Mailloux P, Mulhern J, Ashworth B, Burris J, Brewer B, Nindl B, Coughlin M, Welles R, Jones M. Resistance training improves strength and functional measures in patients with end-stage renal disease. Am J Kidney Dis 2002; 40(2):355-364.
141. DePaul V, Moreland J, Eager T, Clase CM. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am J Kidney Dis 2002; 40(6):1219-1229.
142. Kouidi E, Grekas D, Deligiannis A, Tourkantonis A. Outcomes of long-term exercise training in dialysis patients: comparison of two training programs. Clin Nephrol 2004; 61 (Suppl 1):S31-38.
143. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. Nephrol Dial Transplant 2005; 20(1):141-146.

Chapter 2

Weight changes after renal transplantation: a comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immunosuppressive therapy

ECH van den Ham, JP Kooman, MHL Christiaans, FHM Nieman, JP van Hooff

Transplant International 2003; 16:300-306

Abstract

Background
After renal transplantation, an increase in body weight is usually observed, in which corticosteroids may play an important role. However, the effects of a low maintenance dosage of corticosteroids on body weight have not been studied longitudinally in renal transplant patients. The aim of the study was to compare changes in body weight after renal transplantation in patients on steroid and steroid-free immunosuppressive therapy and to assess the relationship between post-transplant weight changes and other potentially important factors.

Patients and methods
The charts of 123 renal transplant patients (72 males, 51 females) were retrospectively examined for body weight changes in the first five years after renal transplantation. Sixty-six patients were on 5-mg maintenance steroid dose and 57 patients were receiving steroid-free immunosuppression.

Results
Mean post-transplant weight gain was 3.0±5.3 kg after six months, 3.9±6.2 kg after one year, and 6.2±8.6 kg after five years. Weight gain in the first year after renal transplantation was neither related to maintenance nor to cumulative steroid dose, age, gender, occurrence of rejection, or renal function. Weight gain was, however, significantly related to pre-transplant body mass index and dialysis modality. After the first year, weight gain was only significantly and positively related to the cumulative steroid dose.

Conclusions
The course of weight gain in the first year after renal transplantation turned out to be independent from factors such as maintenance or cumulative steroid dose, age, gender, occurrence of rejection, and renal function; weight gain was, however, dependent on pre-transplant body mass index and dialysis modality. After the first year, the weight course was significantly affected by cumulative steroid dose.

Introduction

Malnutrition is common in patients with end-stage renal disease, and is strongly related to morbidity and mortality. The pathogenesis of malnutrition is multifactorial, potential significant factors being reduction in appetite due to uremia, catabolic factors such as acidosis, loss of nutrients in the dialysate, and the presence of a chronic inflammatory state. Most of these factors are corrected by renal transplantation. The nutritional status may improve after transplantation, as usually an increase in body weight is observed. However, it has also been shown that a large part of the post-transplant weight gain is due to an increase in body fat mass[1-5], which may have untoward metabolic and cardiovascular effects[6-8]. The steroid immunosuppressive treatment after renal transplantation may play a role in excessive weight gain and increased fat mass in renal transplant (RTx) recipients. Glucocorticoids are known to have profound effects on adipocytes, resting energy expenditure and lipid oxidation, which can result in centripetal obesity (i.e., increased fat deposition in the peritoneum, mediastinum, and in subcutaneous sites on the face and the neck)[4,9,10]. Besides glucocorticoids, factors such as age, gender, pre-transplant body mass index (BMI) and dialysis modality, the occurrence and treatment of rejection, and post-transplant renal function may be significant in the pathogenesis of weight changes after renal transplantation.
To date, the effects of a low maintenance dosage of corticosteroids on body weight after renal transplantation have not been studied longitudinally. In this study, we therefore analyzed weight changes after renal transplantation in relation to maintenance and cumulative steroid dose. The relationship between other factors possibly affecting body weight (as mentioned above) and post-transplant changes in body weight was also assessed.

Patients and methods

Patients

The charts of all patients who received a kidney graft in our center between January 1982 and December 1994 were examined for weight changes in the first five years after renal transplantation. In this period, 333 patients had undergone transplantation. Of these patients 50 had to (re)start dialysis, and 54 died within five years of undergoing transplantation. A further 33 patients underwent transplantation in the pre-cyclosporine era and were using azathioprine and a high maintenance dose prednisolone (≥10 mg/day). Yet another 15 patients participated in a clinical trial and were treated with tacrolimus immunosuppression. In 82 patients either a non-regular immuno-

suppressive regimen was used (due to, among other things, treatment in hospitals else or protocol violation) or follow-up was lost. Complete data of 123 RTx patients were available for analysis.

Of these 123 patients, 118 had received cadaveric renal allografts and five had received living-(un)related donor renal allografts. Reasons for kidney failure were chronic glomerulosclerosis (31.7%), pyelonephritis (4.9%), nephro-sclerosis (4.1%), polycystic kidney disease (17.9%), diabetes (8.1%), and other (33.3%). Before transplantation, 78 patients were on hemodialysis (HD) and 42 patients were on continuous ambulatory peritoneal dialysis (CAPD); three patients did not undergo renal replacement therapy.

Since the introduction of cyclosporine, the standard immunosuppressive regimen at our center has been cyclosporine and low-dose prednisolone (10 mg/day) for recipients of first grafts. The prednisolone dose is reduced to 7.5 mg/day at month 1 and to 5 mg/day at month 3. In recipients without rejection, the prednisolone dose is further tapered to 0 mg over the next months. For highly immunized recipients (panel reactive antibodies >85%) and re-transplant patients, azathioprine (±1 mg/kg body weight) is added to the above regimen, and the dose of prednisolone is tapered to and maintained at 5 mg/day.

Of the 123 RTx patients, 57 underwent cyclosporine mono-therapy without prednisolone; cyclosporine mono-therapy was started at 7.3±2.6 months after renal transplantation (range 3.7-15.4 months). Further 66 patients were treated with cyclosporine and a maintenance prednisolone dose of 5 mg/day. Of these 66 patients, 46 experienced acute rejection within six months of renal transplantation (the 5-mg pred/rej+ group); in 15 of these 46 patients azathioprine was added to the cyclosporine and 5-mg prednisolone immunosuppressive therapy. The remaining 20 (all re-transplant or highly immunized patients) did not experience any rejections (the 5-mg pred/rej- group). The steroid maintenance dose was reached at 3.5±1.5 months after renal transplantation (range 1.4-7.8 months) in the 5-mg pred/rej+ group and at 3.6±2.9 months (range 1.4-10.1 months) in the 5-mg pred/rej- group.

Clinical characteristics of the patients in the 0-mg maintenance steroid, the 5-mg pred/rej+ and the 5-mg pred/rej- groups are shown in table 2.1. Groups were comparable for age, body weight and BMI before renal transplantation; creatinine clearance (calculated by the formula of Cockcroft[11]) one year after renal transplantation was significantly better in the 5-mg pred/rej- group than in the 0-mg and 5-mg pred/rej+ groups.

Table 2.1 Clinical characteristics of the RTx patients in the 0-mg prednisolone, the 5-mg pred/rej- en 5-mg pred/rej+ group

	0-mg (n=57)	5-mg pred/rej- (n=20)	5-mg pred/rej+ (n=46)
Age (yr)	47.6 ± 12.3	45.7 ± 11.4	42.9 ± 12.8
Gender (M/F)	32 / 25	11 / 9	29 / 17
Body weight before transplantation (kg)	66.0 ± 10.8	67.7 ± 12.7	71.0 ± 15.6
BMI before transplantation (kg/m^2)	22.9 ± 3.0	23.2 ± 3.1	24.6 ± 4.6
Creatinine clearance (ml/min)[a]	55.4 ± 18.4	71.4 ± 17.3[b]	58.9 ± 20.1

Data given as mean ± SD; [a] creatinine clearance one year after transplantation; [b] p<0.01 compared to 0-mg group and p<0.05 compared to 5-mg pred/rej+ group; BMI=body mass index.

Methods

In this retrospective, longitudinal study, we initially studied changes in body weight after renal transplantation. Then, the relationship between post-transplant weight changes and the maintenance steroid dose was assessed. For this purpose, weight changes in RTx patients on 0-mg and 5-mg maintenance prednisolone dose were compared. Of these, the group of patients receiving 5-mg prednisolone maintenance therapy was further divided into patients who experienced rejection episodes (rej+ group) and patients who did not (rej- group). We did this because patients experiencing rejection were receiving steroid boluses, which increased the cumulative steroid dose in the rej+ group (table 2.2). Finally, the relationship between age, gender, pre-transplant BMI, pre-transplant dialysis modality (i.e., HD or CAPD), renal function (creatinine clearance), acute rejection (i.e., occurrence of acute rejection within six months post-transplantation), the cumulative steroid dose, and post-transplant weight changes, was also investigated.

Table 2.2 Cumulative steroid doses (mg) in the 0-mg prednisolone, the 5-mg pred/rej- en 5-mg pred/rej+ group

Time after transplantation	0-mg (n=57)	5-mg pred/rej- (n=20)	5-mg pred/rej+ (n=46)
1 month	384.0 ± 69.8 (377.5)[a]	416.0 ± 63.9 (393.7)[a]	1628.8 ± 1457.4 (487.5)
2 months	624.0 ± 73.9 (612.5)[a]	660.5 ± 53.5 (666.3)[a]	2020.6 ± 1460.8 (1052.5)
3 months	800.5 ± 107.2 (775.0)[a]	863.1 ± 82.5 (857.5)[a]	2308.8 ± 1473.2 (2003.8)
6 months	1070.0 ± 209.1 (1055.0)[a]	1389.4 ± 195.8 (1330.0)[a]	2808.5 ± 1482.5 (2450.0)
12 months	1198.7 ± 375.8 (1058.8)[ab]	2320.7 ± 252.2 (2240.0)[a]	3842.4 ± 1470.8 (4093.8)
60 months	1293.8 ± 595.8 (1063.8)[ab]	9639.4 ± 260.9 (9549.3)[a]	11361.5 ± 1796.0 (11408.8)

Data given as mean ± SD (median); [a] p<0.001 compared to 5-mg pred/rej+ group; [b] p<0.001 compared to 5-mg pred/rej- group.

Baseline body weight was measured at admission, prior to transplantation; CAPD patients were measured while their abdomen was empty. In the first

year after renal transplantation, the body weight of the patients was measured at months 1, 2, 3, 6, 9 and 12. Thereafter, body weight was assessed each year (24, 36, 48 and 60 months after transplantation). Patients were weighed (wearing only underwear) during routine visits to the nephrology outpatient clinic in our hospital.

Statistics

Results were expressed as mean±SD. Comparisons of the clinical characteristics between the RTx patients in the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ groups were performed by means of one-way ANOVA analysis; pairwise multiple comparisons were corrected via post hoc Bonferroni tests.
Post-transplant changes in body weight within the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ groups (= within factor = factor 'time'), as well as within-patients differences between these three groups (= between factor = factor 'group'), were analyzed by means of two-way repeated measures ANOVA. In this way the effects of the factor 'time', 'group' and of the interaction term 'time by group' were determined. A significant 'time' factor means that body weight significantly changes over the time period; a significant 'time by group' interaction term points to differences in body weight course between the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ group. Reversed Helmert contrasts were sometimes used to test differences with the baseline. Apart from this, body weight 12 months after renal transplantation was used as baseline to analyze post-first-year changes in body weight.
Possible disturbing or modifying effects on post-transplant weight course caused by different variables were analyzed next, by means of two-way repeated measures ANCOVA if the potential confounding variable was of interval or ratio measurement level, and by two-way repeated measures ANOVA if a potential confounding factor was involved. Confounding factor interrelations appeared at one instance so relevant for weight changes that both were introduced simultaneously within the ANOVA model: the interaction term of both confounders with weight changes was inspected. Statistical analysis was performed by SPSS for Windows, version 9.0.

Results

Weight gain after renal transplantation

The mean baseline (pre-transplant) body weight in the RTx patients (n=123) was 68.2±13.2 kg. In the first month after transplantation, body weight decreased significantly to 67.4±12.7 kg ($p<0.05$). After this, patients started to

gain weight. Two months after transplantation, patients returned approximately to their baseline body weight. After the first three months, the body weight of the RTx patients had increased to 72.1±12.0 kg (+6.7±9.9%) one year after transplantation ($p<0.001$) and to 74.4±14.0 kg (+10.0±13.5%) five years after transplantation ($p<0.001$). The F-ratio for weight gain (=factor 'time') in the first year after transplantation was $F_{(2,262)}=62.35$ ($p<0.001$), and for weight gain after the first year it was $F_{(3,331)}=11,38$ ($p<0.001$).

Steroid immunosuppression and post-transplant weight changes

Post-transplant changes in body weight in the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ groups are given in figure 2.1. The F-ratio for weight gain in the first year after transplantation was $F_{(2,256)}=55.47$ ($p<0.001$), and for weight gain after the first year it was $F_{(3,331)}=10.34$ ($p<0.001$). Body weight course in the first year after transplantation, and post-first-year body weight course were not significantly different between patients in the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ groups. In the first year after transplantation, body weight significantly increased from 67.8±12.7 kg (baseline) to 72.8±11.9 kg (+8.5±11.0%) in the 5-mg pred/rej- group ($p<0.01$), from 71.0±15.6 kg (baseline) to 74.3±14.5 kg (+5.8±10.7%) in the 5-mg pred/rej+ group ($p<0.01$), and from 66.0±10.8 kg (baseline) to 70.0±9.4 kg (+6.8±8.8%) in the 0-mg group ($p<0.001$). After the first year, body weight gradually increased to 75.2±13.8 kg (+3.1±7.3%) in the 5-mg pred/rej- group ($p=0.07$), to 77.9±16.8 kg (+4.7±8.0%) in the 5-mg pred/rej+ group ($p<0.001$) and to 71.2±10.8 (+1.7±7.0 %) in the 0-mg group ($p=0.08$) at five years after transplantation.
Cumulative doses of steroids also had no relation whatsoever with the post-transplant weight course of RTx patients in the first year after transplantation. The cumulative steroid dose, however, did significantly affect the linear trend for weight course after the first year after transplantation: the higher the cumulative steroid dose, the higher the weight gain.

Relationship between age and gender and post-transplant weight changes

The post-transplant course of body weight was not related to the age of the RTx recipients, nor was it significantly different for men and women.

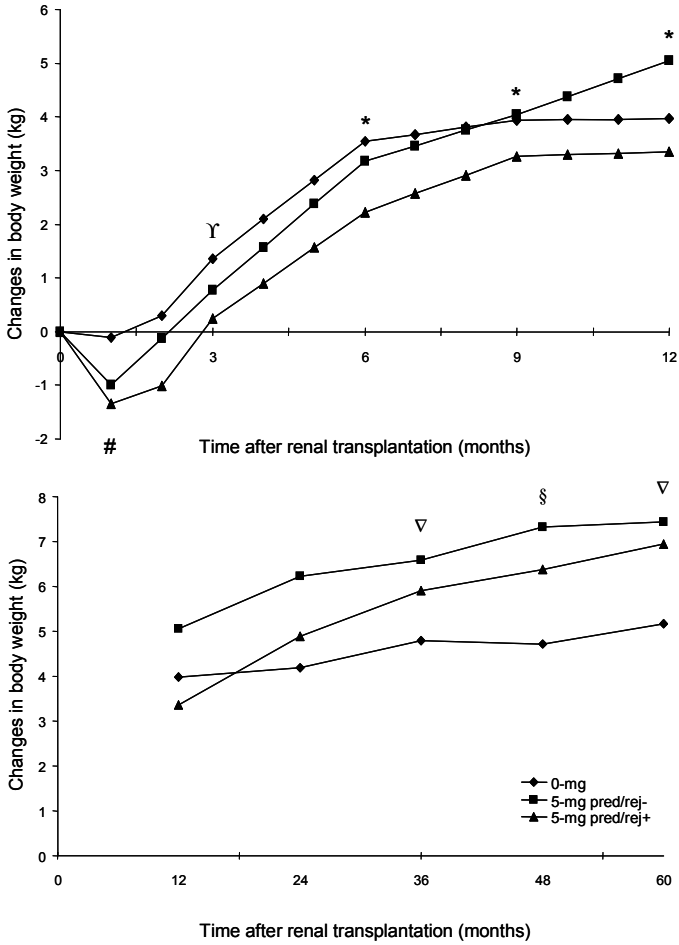


Figure 2.1 Weight changes in the first year and after the first year post-transplantation in the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ group.

* p<0.05 compared with baseline in the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ groups;

\# p<0.05 compared with baseline only in the 5-mg pred/rej+ group;

ϒ p<0.05 compared with baseline only in the 0-mg group;

∇ p<0.05 compared with month 12 only in the 5-mg pred/rej+ group;

§ p<0.05 compared with month 12 only in the 5-mg pred/rej+ and 5-mg pred/rej- groups.

Relationship between pre-transplant BMI, dialysis modality and post-transplant weight changes

At baseline, 16 RTx patients (13.0%) had a BMI <20 kg/m^2, 73 patients (59.3%) had a BMI between 20 and 25 kg/m^2, and 32 patients (26.0%) had a BMI>25 kg/m^2; mean body weight in these groups was 52.9±5.5 kg, 65.4±8.6 kg and 83.1±10.7 kg, respectively (p<0.001). Weight gain in these three groups during the first year after transplantation appeared to be significantly different ($F_{time*BMI\text{-}group\ (5,268)}$ =7.57; p<0.001): patients with a BMI>25 kg/m^2 had a significantly lower weight gain (0.8±8.0%) than patients with a BMI between 20 and 25 kg/m^2 (7.4±9.2%, p<0.05) and patients with a BMI<20 kg/m^2 (16.0±8.3%, p<0.001 compared with BMI>25 kg/m^2 and BMI 20-25 kg/m^2). Next to this result, at baseline, the 78 patients who had HD had a significantly lower weight than the 42 patients who had CAPD (65.8±12.1 kg versus 73.0±14.2 kg, p<0.01). Weight gain during the first year after transplantation in these two groups was also significantly different ($F_{time*dialysis\ modality\ (2,256)}$=4.02, p<0.05): patients with CAPD had a significantly lower weight gain than patients with HD. However, as shown in figure 2.2, the latter result seems to be valid only for RTx patients with a BMI>25 kg/m^2. Pre-transplant BMI was highly related to pre-transplant dialysis modality (mean BMI in HD versus CAPD patients was 23.0±3.2 kg/m^2 versus 24.8±4.5 kg/m^2, p<0.05). So, as a next step, we introduced both BMI group and dialysis modality as factors in the ANOVA weight-gain model. The interaction effect 'time*dialysis modality*BMI group' was, however, not significant ($F_{(5,257)}$=2.08, p=0.08). Thus, in conclusion, patients with a low pre-transplant BMI gain significantly more weight in the first year after transplantation than patients with higher BMI's, irrespective of pre-transplant dialysis modality. Neither pre-transplant BMI nor dialysis modality had any effect on the body weight course after the first year.

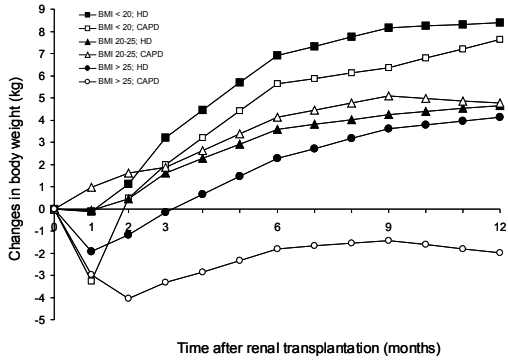


Figure 2.2 Post-transplant changes in body weight in RTx patients with a pre-transplant BMI<20 kg/m^2 (n=16), 20-25 kg/m^2 (n=73) and >25 kg/m^2 (n=32).

Relationship between acute rejection and post-transplant weight changes

Forty-six patients experienced an acute rejection within six months of transplantation. On the average, the rejection episodes occurred 12.4±10.9 days (range 1-56 days; median 8.0 days) days post-transplantation. The body weight course in the first year after transplantation and the weight course after the first year were not significantly different for patients with or without a history of acute rejection.

Relationship between renal function and post-transplant weight changes

In the first year after transplantation, at none of the time points of measurement was the average weight gain significantly related to the creatinine clearance. The mean creatinine clearance of the patients (n=123) one year after transplantation was 59.3±19.5 ml/min. To facilitate the analysis, we divided the RTx patients into two groups, to assess the relationship between renal function (i.e., creatinine clearance) and post-transplant weight gain. Group I consisted of RTx patients with a creatinine clearance ≤50 ml/min one year after transplantation (n=45); group II consisted of patients with a creatinine clearance >50 ml/min one year after transplantation (n=78). The body weight course in the first year after transplantation and the post-first-year weight course were not significantly different for groups I and II.

Discussion

In this study, changes in body weight after renal transplantation were studied. Furthermore, the relationship between post-transplant weight changes and the maintenance prednisolone dose was assessed. Relationships between post-transplant weight changes on the one hand, and age, gender, pre-transplant BMI, pre-transplant dialysis modality, renal function, acute rejection and the cumulative dose of steroids on the other hand, were also investigated.

In the first month after transplantation, patients on the average lost body weight. This could be due to catabolic effects of surgery, loss of excess fluid, delayed graft function, or decreased dietary intake in the early post-transplant period. After the first month after transplantation, patients started to gain weight, which resulted in a mean increase in body weight of 3.0 kg at six months after transplantation, 3.9 kg at one year and 6.2 kg at five years after transplantation. Post-transplant weight gain was, however, relatively low when compared with the weight gain reported in other studies[11-14]. One explanatory

factor might be the relative low steroid dose in our study. Moore et al.[14] found a mean weight gain of 4.0 kg during the first six months after transplantation in a group of patients treated with 0.5 mg steroids per kg ideal body weight (IBW) in the first three months after renal transplantation and with 0.2 mg steroids per kg IBW after the first three months. Merion et al.[13] found an average weight gain of 8.9 kg in non-obese patients and 14.2 kg in obese patients during the first year after renal transplantation; both the obese and non-obese patients underwent immunosuppressive therapy with high dosages of corticosteroids (10 mg/day), cyclosporine and azathioprine.
Excessive weight gain, a major problem for many RTx patients, is associated with an increased risk of metabolic and cardiovascular complications, a major cause of morbidity and mortality in RTx patients[6-8,16]. Some weight gain might be favorable in patients who were malnourished at the point of transplantation. In an earlier prospective pilot study[17], however, we observed that weight gain in the early post-transplant period (at least until six months after renal transplantation) was predominantly due to an increase of the body fat mass, and not to an increase of the lean body mass.

In the present study, no differences were found in body weight course of patients in the 0-mg, 5-mg pred/rej- and 5-mg pred/rej+ groups in the first year and after the first year after renal transplantation, and no relationship was observed between first year post-transplant weight gain and the cumulative steroid dose. Cumulative steroid dose was, however, significantly and positively related to post-first-year weight gain.
Johnson et al.[18] did not find a significant relationship between post-transplant weight gain and cumulative steroid dose one year after renal transplantation either, whereas the cumulative dose was substantially higher than that in our study. Conversely, Ratcliffe et al.[19] found, in a randomized controlled trial, that RTx patients allocated to the prednisolone withdrawal group had a slight but significant reduction in body weight, whereas over the same period there was a slight increase of body weight in the control group. Hagan and collegues[20] found that successful withdrawal of maintenance corticosteroids in the first year after heart transplantation decreased post-transplant weight gain. On the other hand, neither Lake et al.[21] nor Olivari et al.[22] observed significant differences in weight gain after heart transplantation between patients undergoing prednisolone therapy and patients tapered from prednisolone therapy. Evidently, the results are conflicting, and more prospective studies are needed to assess definitively the influence of low-dose steroids on post-transplant weight gain.
In this study, only body weight was assessed. Therefore, differences in body composition between the various prednisolone groups in the study cannot be excluded. However, in an earlier cross-sectional study on 75 RTx patients in

our center, no differences in body fat mass were observed whether the daily maintenance steroid dose was 10-mg, 5-mg or 0-mg prednisolone. Furthermore, no relationship between the cumulative dose of prednisolone and body composition was observed[23]. Nevertheless, the increase in body fat between three and six months after renal transplantation tended to be lower in patients undergoing steroid-free immunosuppressive therapy than in patients receiving steroid immunosuppressives[24]. Prospective randomized studies are therefore needed to assess more precisely the influence of low-dose maintenance steroid therapy on weight gain and body composition in RTx patients.

We did not find a relationship between age and gender, respectively, and post-transplant weight gain. This is in contrast with the study by Johnson et al.[18] who found a comparable weight gain in men and women during the first year after renal transplantation, although women continued to gain weight after the first year and men remained relatively stable. Johnson et al.[18] also found a larger weight gain in younger patients (18-29 years) than in middle-aged (30-49 years) and older patients (>50 years). In agreement with the results of our study, Moore et al.[14] found no difference in weight gain between men and women in the first six months after renal transplantation.
A difference in weight course between patients with or without rejection episodes or in patients with well-functioning grafts or with decreased renal function, might be expected. Factors accompanying by rejection episodes and decreased renal function, such as (prolonged) hospitalization, increased stress, prolonged effects of uremia, catabolism, feeling of malaise, or decreased appetite, might affect weight course after renal transplantation. In the present study, however, we did not find any relationship between post-transplant weight changes and acute rejection or renal function, which is consistent with the results of Johnson et al.[18]. In contrast, Moore et al.[14] noticed that the occurrence of rejection episodes in patients who lost body weight in the first six months after renal transplantation was significantly higher than in patients who gained weight during this period.
In the present study, we initially found differences in weight course in the first year after transplantation between patients with a pre-transplant BMI<20 kg/m^2, BMI 20-25 kg/m^2, and BMI>25 kg/m^2 and also between pre-transplant HD and CAPD patients, the latter experiencing a significantly lower weight gain than the HD patients. Although pre-transplant BMI was significantly higher in CAPD patients than in HD patients, no significant interaction effect of pre-transplant BMI and pre-transplant dialysis modality on post-transplant weight course appeared to be in existence. The larger increase in body weight in patients with low BMI might be explained by an improvement in their nutritional state, although this cannot be definitively determined from the available data. This

again highlights the importance of detailed data on body composition in future nutritional studies.

Conclusions

RTx patients started to gain weight from the first month after renal transplantation, after loosing weight in the first month. In the first year after transplantation, the increase in body weight was related neither to maintenance nor cumulative steroid dose, whereas in the later post-transplant period, cumulative steroid dose appeared to have a significant effect on body weight increase. Post-transplant weight gain was not related to age, gender, episodes of rejection or renal function. Weight gain in the first year after renal transplantation was, however, significantly related to pre-transplant BMI and dialysis modality. More detailed data are needed to definitively assess the influence of relatively low maintenance doses of corticosteroids on post-transplant body weight course and body composition.

References

1. Hart PD, Wilkie ME, Edwards A, Cunningham J. Dual energy X-ray absorptiometry versus skinfold measurements in the assessment of total body fat in renal transplant recipients. Eur J Clin Nutr 1993; 47:347-52.
2. Isiklar I, Akin O, Niron EA. Effects of renal transplantation on body composition. Transplant Proc 1998; 30:831-832.
3. Martin M, Lopes IM, Errasti P, Martinez JA. Body composition and biochemical profile as affected by diet and renal transplantation among renal patients. J Physiol Biochem 1998; 54: 53-54.
4. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger Ph, Horber FF. Body composition and fuel metabolism after kidney transplantation. Eur J Clin Invest 1995; 25:809-816.
5. Verran D, Munn S, Collins J, Hill G. Impact of renal allograft implantation and immunosuppression on body composition using in vivo neutron activation analysis. Transplant Proc 1992; 24:173-174
6. Gunnarson R, Lofmark R, Nordlander R, Nyquist O, Groth CG. Acute myocard infarction in renal transplant recipients: incidence and prognosis. Eur Heart J 1984; 5:218-221.
7. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7:158-165.
8. Raine AEG, Margreiter R, Brunner FP, Ehrich JH, Geerlings W, Landais P, Loirat C, Mallick NP, Selwood NH, Tufveson G. Report of managment of renal failure in Europe, XXII 1991. Nephrol Dial Transplant. 1992; 7(Suppl 2):7-35.
9. Danovitz GM. Immunosuppressive medications and protocols for kidney transplantation. In: Danovitz GM (ed). Handbook of kidney transplantation. Little Brown and Compagny, Boston, 1992:67-104.
10. Yanovski JA, Gordon BC. Glucocorticoid action and the clinical features of Cushing's syndrome. Endocrinol Metab Clin North Am 1994; 23:487-509.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
12. Gonyea JE, Anderson CF. Weight change and serum lipoproteins in recipients of renal allografts. Mayo Clin Proc 1992; 67:653-657.
13. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, Rocher LL, Campbell DA. Obesity and renal transplantation. Surg Gynecol Obstet 1991; 172:367-376.
14. Moore LW, Gaber AO. Patterns of early weight change after renal transplantation. J Ren Nutr 1996; 6:21-25.
15. Patel MG. The effect of dietary intervention on weight gains after renal transplantation. J Ren Nutr 1998; 8:137-141.
16. Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: 13 year follow-up of participants in the study of men born in 1913. BMJ 1984; 288:1401-1404.
17. van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP. Post transplantation weight gain is predominantly due to an increase in body fat mass. Transplantation 2000; 70:241-242.
18. Johnson JP, Gallagher-Lepak S, Zhu Y, Porth C, Kelber S, Roza AM, Adams MB. Factors influencing weight gain after renal transplantation. Transplantation 1993; 56:822-827.
19. Ratcliffe PJ, Dudley CRK, Higgins RM, Firth JD, Smith B, Morris PJ. Randomised controlled trial of steroid withdrawal in renal transplant patients receiving triple immunosuppression. The Lancet 1996;348: 643-648.
20. Hagan ME, Holland CS, Herrick CM, Rasmussen LG. Amelioration of weight gain after heart transplantation by corticosteroid-free maintenance immunosuppression. J Heart Transplant 1990; 9:382-384.
21. Lake, KD, Reutzel TJ, Pritzker MR, Jorgensen CR, Emery RW. The impact of steroid withdrawal on the development of lipid abnormalities and obesity in heart transplant recipients. J Heart Lung Transplant 1993; 12:580-590.

22. Olivari MT, Jessen ME, Baldwin BJ, Horn VP, Yancy CW, Ring WS, Rosenblatt RL. Triple-drug immunosuppression with steroid discontinuation by six months after heart transplantation. J Heart Lung Transplant 1995; 14:127-135.
23. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation 2000; 69:1591-1598.
24. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. The influence of early steroid withdrawal on body composition and bone mineral density in renal transplant patients. Transpl Int 2003; 16:82-87.

Chapter 3

Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry

ECH van den Ham, JP Kooman, MHL Christiaans, FHM Nieman, BK van Kreel, GAK Heidendal, JP van Hooff

Journal of the American Society of Nephrology 1999; 10:1067-1079

Abstract

Background
Whether multi-frequency bio-electrical impedance analysis (MF-BIA), a relatively new method for measuring body composition, is also applicable for accurate body composition measurements in renal transplant patients is not known. Therefore, the use of MF-BIA is validated in 77 renal transplant patients with a stable renal function at least two years post-transplantation.

Methods
MF-BIA is compared to isotope dilution techniques for measurement of body water compartments, and to dual energy x-ray absorptiometry (DEXA) and anthropometry for measurement of fat and fat-free mass. Finally, DEXA and anthropometry are compared to each other. Method agreement is assessed by intraclass correlation coefficients (ICC) and plotted by Bland and Altman analysis.

Results
MF-BIA significantly underestimates total body water (TBW, 0.7±2.1 liter) and over-estimates the extra-cellular water (ECW, 3.3±1.8 liter) compared to isotope dilution; the ICC between both techniques is 0.943 for TBW and 0.846 for ECW. The percentage body fat measured by MF-BIA is significantly higher than both body fat measured by DEXA (3.4±4.7%) or by anthropometry (5.5±5.2%). The ICC between MF-BIA and DEXA is 0.887 and between MF-BIA and anthropometry 0.856. Body fat measured by DEXA is significantly higher than body fat measured by anthropometry (2.1±4.4%); their ICC is 0.913.

Conclusions
MF-BIA seems to be suitable for measurement of TBW in renal transplant patients; however, method agreement between isotope dilution and MF-BIA for the measurement of ECW is not satisfactory. In the assessment of fat and fat-free mass, the reliability of MF-BIA appears to be questionable. Method agreement between DEXA and anthropometry seems to be slightly better.

Introduction

Renal transplant (RTx) patients are at risk for increased weight, centripetal obesity, and muscle atrophy because of their long-term glucocorticoid requirements[1-5]. Such changes in body composition are associated with an increased risk of cardiovascular complications[1,6-10], a major cause of morbidity and mortality in RTx patients[11-16]. Body composition data might provide insight into the relation with outcome, survival and post-transplant complications; it might also affect approaches to nutritional therapy and to therapy in the field of physical activity.

Various techniques are available to measure body composition, among them isotope dilution, anthropometry, dual energy x-ray absorptiometry (DEXA) and multi-frequency bio-electrical impedance analysis (MF-BIA). MF-BIA is recently introduced for measuring body composition. It is a relatively inexpensive, noninvasive, easy to use, and portable technique, and therefore suitable for routine clinical use.

MF-BIA is considered to be a useful technique for body composition analysis in healthy individuals[17]. However, it is not known whether MF-BIA is also applicable for accurate body composition measurements in RTx patients. In this study we validated MF-BIA for its use in RTx patients by comparing MF-BIA to isotope dilution, which is considered the gold standard for measuring body water compartments in healthy individuals. Furthermore, we compared MF-BIA, DEXA, and anthropometry to one another for measurement of the body fat and fat-free compartment.

Patients and methods

Patients

RTx patients with a stable renal function and maintenance immunosuppressive therapy for at least two years were studied. Exclusion criteria were insulin-dependent diabetes mellitus, metal implants (prostheses or pacemakers) and recent complications (e.g., malignancies or surgery). All patients were receiving immunosuppressive therapy, which consisted of combinations of prednisolone, azathioprine, and cyclosporine.

Informed consent was obtained from each patient, and the study was approved by the Ethical Committee of the Maastricht University Hospital.

Methods

In this cross-sectional study, body composition was measured by isotope dilution (deuterium (D_2O) and potassium bromide (KBr)), DEXA, anthropometry, and MF-BIA (figure 3.1).

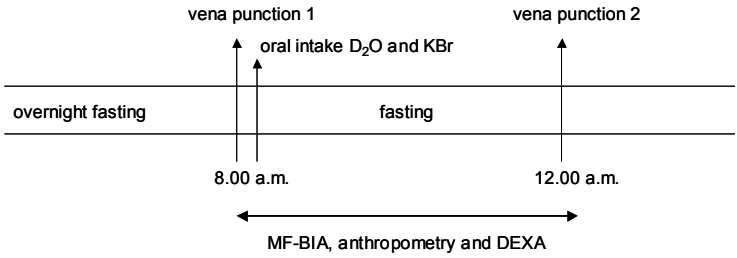


Figure 3.1 Study design.

Isotope dilution

In the early morning after an overnight fast, patients received an orally administered dose of D_2O of 25 ml (99%, Sigma Chemicals, St. Louis, MO) and KBr of 30 ml (150 mM). Dose bottles were rinsed out and the rinse water was also ingested by the patients to ensure that all D_2O and KBr was consumed. Enrichments of D_2O and KBr in the body fluid were measured in serum. Immediately before D_2O and KBr intake, a (background) blood sample was taken. After an equilibration time of four hours, a second blood sample was collected. Food intake was not allowed until the second blood sample was collected; nevertheless, drinking some small amounts of water was allowed as all patients had to take their immunosuppressive medication just before or during measurements.

The concentration of D_2O and bromide in serum was determined by isotope ratio mass spectrometry and ion chromatography, respectively[18,19]. D_2O and bromide dilution spaces were calculated from the enrichment of D_2O and bromide after four hours, respectively[20]. Total body water (TBW) was calculated as the D_2O dilution space corrected for the exchange of D_2O with non-aqueous compartments and for the concentration of water in the serum by first dividing the dilution space by 1.04 and thereafter multiplying it by 0.94[20,21]. The extra-cellular water (ECW) compartment was calculated as the bromide dilution space corrected for intracellular penetration of bromide in erythrocytes, leukocytes, and secretory cells; for unequal bromide concentrations in the extra-cellular fluids (Gibbs-Donnan effect); and for the concentration of water in the serum; therefore, bromide dilution space was multiplied by 0.90*0.95*0.94, respectively[20,22-25].

Dual energy x-ray absorptiometry (DEXA)

DEXA was used for measurement of whole-body composition, including fat mass (FM), lean soft tissue mass (comprising muscle, inner organs, and body water) and bone mineral content. The equipment used in this study was DPX-L (Lunar Radiation Corp., Madison, WI).

DEXA measurements were performed in a standard manner while the patient was lying in a supine position on a table. From an x-ray source and K-edge filter below the patient, x-ray beams of stable energy radiation of 38 and 70 KeV were emitted. Attenuation of the x-rays was measured with a detector situated above the patient. Transverse scans of the body were made from top to toe. For each transverse scan, about 120 pixel elements with a size of approximately 5*10 mm yield data on the attenuation ratio. Approximately 40 to 45% of the pixels over the body contain bone and soft tissue, and 55 to 60% contain soft tissue alone[26]. Bone mass was estimated from the ratio of the attenuation at low energy peaks relative to attenuation at high energy peaks through bone containing pixels after correction for the overlying soft tissue. The composition of the soft tissue was estimated by the ratio of beam attenuation at lower energy relative to the higher energy in soft tissue pixels; this ratio is inversely and linearly related to the percentage fat[26,27].

Anthropometry

Body weight was measured to the nearest 0.1 kg using a balance scale. Body height was measured to the nearest 0.5 cm with the patient standing, back to a stadiometer.

Skinfold measurements were used to estimate total body FM. Skinfold thickness was measured to the nearest 0.1 mm by a skinfold caliper. Measurements were made at the nondominant side of the body at four sites: biceps, triceps, subscapula and iliac crest. Skinfolds were measured three times. Thereafter, the sum of the individual skinfolds was averaged. The logarithm of the sum of the four skinfolds was used in age- and gender specific regression equations of Durnin and Womersly[28] to compute body density (D). FM was computed as body weight (kg) * ((4.95/D)-4.5); fat-free mass (FFM) (kg) as body weight (kg) - FM (kg)[28,29].

Waist circumference was measured midway between the lower rib margin (costal margin) and the superior anterior iliac spine (iliac crest). Hip circumference was measured at the level of the great trochanters. Both waist and hip circumference were measured to the nearest millimeter with a flexible tape, with the patient in standing position.

Multi-frequency bio-electrical impedance analysis

Bio-electrical impedance measurements were performed in a standard manner while the patient was lying supine on a flat, nonconductive bed. Multi-frequency

(5 to 500 KHz), imperceptible currents were introduced at distal electrodes on the hands (just proximal to the phalangeal-metacarpal joint in the middle of the dorsal side of the hand) and the feet (just proximal to the transverse (metatorsal) arch on the superior side of the foot), and resistances were measured by proximal electrodes (to the wrist midway between the styloid process, to the ankle midway between the malleoli). TBW and ECW were predicted from a general mixture theory (theory of Hanai)[30-32]: water compartments are directly calculated from resistance values, assuming specific resistances of ECW and intracellular water (ICW). Specific resistances of ECW and ICW are provided by the manufacturer (for men: ρECW=215.0, ρICW=824.0; for women ρECW=206.0, ρICW=797.0). The bio-electrical impedance analyser used in this study was the Xitron 4000B (Xitron Technologies Inc., San Diego, CA). FFM is derived from the ECW and ICW volume; FM is calculated as body weight minus FFM[33].
To determine the reproducibility of MF-BIA measurements, the MF-BIA measurement was performed twice in a small number of patients (n=10); precision was assessed by calculating the mean coefficient of variation of duplicate measurements (coefficient of variation = (standard deviation of the two measurements / mean of the two measurements) * 100%).

Statistics

Paired *t* tests were used to compare TBW and ECW measured by isotope dilution to TBW and ECW measured by MF-BIA and to compare body fat (BF) measured by MF-BIA to BF measured by DEXA and anthropometry, respectively. Correlations between body compartments measured by different methods were estimated by the use of Pearson product moment correlations. A p-value <0.05 was considered significant. Bland and Altman plots[34,35] were used to visually assess agreement between the different methods to measure TBW, ECW, and BF, respectively. In addition to these, the intraclass correlation coefficient (ICC) was calculated using variance components generated from repeated measurements ANOVA. The ICC can be interpreted as a measure of agreement between methods and will vary from 0 (no agreement at all) to 1 (perfect agreement). Lowest acceptable method agreement was defined as 0.85. According to Fleiss[36], an approximate one-sided 95% lower confidence level for the ICC can be calculated to ascertain whether it satisfies the predetermined level of agreement. Smallest detectable differences (SDD) are used to calculate the limits of agreement at a 5% level. To ascertain whether method agreement varied over important covariates or factors of the patient population (among other things creatinine clearance, the use of calcium antagonists, and the presence of cystic kidneys in patients with polycystic kidney disease (PCKD)), ICC values were also calculated for subcategories of

covariates or factors to see whether method agreement increases or declines in certain subcategories. For this purpose, covariates were categorized into three classes containing one-third of the patients (about 22 to 25 per class), using cutting points as defined in table 3.1. Statistical analysis was performed by SPSS for windows, version 7.5.

Table 3.1 Definition of cutting points used to obtain three subcategories in covariates

	Lowest 33%	Middle 33%	Highest 33%
Age (yr)	≤45.0	45.0 – 57.0	>57.0
BMI (kg/m^2)	≤22.5	22.5 – 26.0	>26.0
Waist-to-hip ratio	≤0.83	0.83 – 0.93	>0.93
Hydration status LBM (l/kg) [a]	≤0.6900	0.6900 – 0.7292	>0.7292
Ratio ECW to ICW [b]	≤0.7651	0.7651 – 0.8950	>0.8950
Creatinine clearance (ml/min)	≤50.76	50.76 – 70.50	>70.50

[a] calculated as TBW measured by deuterium isotope dilution divided by LBM measured by DEXA; [b] ECW measured by bromide isotope dilution ICW calculated as TBW minus ECW (both TBW and ECW measured by isotope dilution); BMI=body mass index; LBM=lean body mass; ECW=extracellular water; ICW=intracellular water.

Results

Patient characteristics

Seventy-seven RTx patients (42 males, 35 females) with a stable renal function participated in the study. Patient characteristics are shown in table 3.2. Mean age of the population was 51.0±11.7 years. Body mass index (BMI) of the transplant patients was 24.8±4.8 kg/m^2. Mean follow-up time after transplantation was 9.1±4.3 years, the mean creatinine clearance was 60.2±20.5 ml/min. On average, patients used a cumulative dose prednisolone of 19.3±21.5 g.

Reproducibility of MF-BIA measurements

Repeated MF-BIA measurements were performed in 10 RTx patients (five males, five females), with a mean age of 59.0±13.1 year and a mean BMI of 23.7±5.1 kg/m^2. The mean coefficient of variation (CV) of the TBW measurements is 1.0% (range individual CV: 0.0 to 2.9%) and of the ECW measurements 0.6% (range individual CV: 0.0 to 1.9%).

Table 3.2 Patient characteristics (n=77)

	Mean ± SD	Range
Age (yr)	51.0 ± 11.7	25.5 – 78.2
Height (m)	1.68 ± 0.10	1.51 – 1.86
Body weight (kg)	69.8 ± 12.8	43.5 – 99.5
BMI (kg/m^2)	24.8 ± 4.8	16.7 – 42.2
Follow-up after transplantation (yr)[a]	9.1 ± 4.3	2.2 – 22.9
Creatinine clearance (ml/min)[b]	60.2 ± 20.5	19.2 – 114.0
Cumulative dose prednisolone (g)	19.3 ± 21.5	0.5 – 83.4

[a] follow-up after transplantation=time lapse post-transplantation; [b] creatinine clearance calculated by the formula of Cockcroft[37]: for males: creatinine clearance=((140-age(yr)) * weight (kg))/(0.81* serum creatinine (μmol/liter)), for females: creatinine clearance=(((140-age(yr)) * weight (kg))/(0.81* serum creatinine (μmol/liter)))*0.85; BMI=body mass index.

Total body water

For 73 RTx patients, data of D_2O dilution are available; data of four patients were lost during laboratory analysis. Descriptive statistics (mean, SD, and range) of TBW measured by D_2O dilution (TBW_{D2O}) and TBW measured by MF-BIA ($TBW_{MF\text{-}BIA}$) are shown in table 3.3. TBW_{D2O} compared with $TBW_{MF\text{-}BIA}$ is 34.2±6.1 liter *versus* 33.5±5.9 liter ($p<0.05$). TBW_{D2O} is highly and significantly correlated to $TBW_{MF\text{-}BIA}$ ($r=0.943$, $p<0.001$). The regression plot of TBW_{D2O} and $TBW_{MF\text{-}BIA}$ is given in figure 3.2. In figure 3.3 the Bland and Altman analysis is plotted. The mean difference between TBW_{D2O} and $TBW_{MF\text{-}BIA}$ is 0.7 liter (95% confidence interval (CI): 0.2 to 1.2 liter). The limits of agreement (mean±2 SD) show that $TBW_{MF\text{-}BIA}$ may be 3.4 liter higher or 4.8 liter lower than TBW_{D2O}.

Table 3.3 Total body water, extra-cellular water and body fat measured by different techniques in RTx patients

	Mean	SD	Range	N[a]
TBW_{D2O} (liter)	34.2	6.1	22.4 – 50.2	73
$TBW_{MF\text{-}BIA}$ (liter)	33.5	5.9	19.3 – 48.4	73
ECW_{KBr} (liter)	15.5	2.9	10.4 – 24.3	72
$ECW_{MF\text{-}BIA}$ (liter)	18.7	3.6	11.1 – 29.0	72
BF_{DEXA} (%)	30.3	10.5	9.0 – 58.0	75
$BF_{MF\text{-}BIA}$ (%)	33.7	9.2	8.0 – 54.2	75
$BF_{anthropometry}$ (%)	27.9	10.2	8.4 – 48.0	74
$BF_{MF\text{-}BIA}$ (%)	33.4	9.2	8.0 – 54.2	74
BF_{DEXA} (%)	30.2	10.7	9.0 – 55.8	72
$BF_{anthropometry}$ (%)	28.1	10.3	8.4 – 48.0	72

[a] the number of patients in each comparison differs due to missing values (see text); TBW=total body water; ECW=extra-cellular water; BF=body fat.

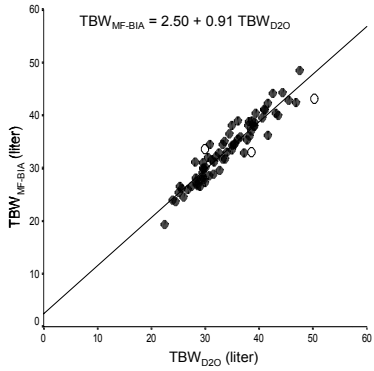


Figure 3.2 Regression plot of TBW_{D2O} and TBW_{MF-BIA}. Outliers (standardized z-residu scores <-2 or >2) are given as open circles.

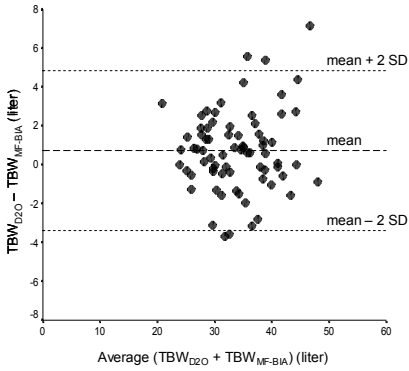


Figure 3.3 Assessment of TBW by D_2O dilution against MF-BIA (Bland and Altman analysis). The relative bias (dilution minus MF-BIA) plotted against the size of the measurement (mean of dilution and MF-BIA).

Table 3.4 shows the ICC for measurement of agreement between TBW_{D2O} and TBW_{MF-BIA} (ICC_{TBW}) and the calculation of this ICC. ICC_{TBW} is 0.943 (95% limits of agreement: -3.3 to 4.8 liter). The approximate one-sided 95% lower confidence level for the ICC according to Fleiss[36] turns out to be 0.916. Table 3.5 shows the ICC values for the subcategories. The agreement between the methods appears to vary little over age, BMI, waist-to-hip ratio, hydration status of the lean body mass (LBM), the ratio ECW to ICW, creatinine clearance, gender or the use of calcium antagonists. All ICC values are larger than 0.892. The ICC_{TBW} in patients with cystic kidneys is 0.886, whereas the ICC_{TBW} in patients without cystic kidneys seems to be higher (0.950).

Table 3.4 Analysis of variance for RTx patients measured twice on TBW (by D_2O dilution and MF-BIA) and ECW (by KBr dilution and MF-BIA) supplemented with estimation of variance components

TBW by D_2O dilution and MF-BIA (n=73)					
Sources of Variation	SS	df	MS	EMS = σ^2	ICC / proportion
Patients (P)	5157.97	72	71.64	34.76	0.943
Method (M)	19.00	1	19.00	(0.23)	-
P * M (error)	152.65	72	2.12	2.12	0.057
Total		145		36.88	1.000
ECW by KBr dilution and MF-BIA (n=72)					
Sources of Variation	SS	df	MS	EMS = σ^2	ICC / proportion
Patients (P)	1396.83	71	19.67	9.02	0.846
Method (M)	379.76	1	379.76	(5.25)	-
P * M (error)	116.48	71	1.64	1.64	0.154
Total		143		10.66	1.000

SS=sums of squares; df=degrees of freedom; MS=mean sum of squares; EMS=expected mean sum of squares; ICC=intraclass correlation coefficient.

EMS=σ^2=(estimated) variance component (VC).

ICC=method agreement=proportion of patient VC to the total amount of patient VC plus the patient-by-method VC, or ICC=σ^2_P / (σ^2_P + σ^2_{P*M}).

For TBW: σ^2_P = (MS $_P$ – MS $_{P*M}$) / 2
σ^2_M = (MS $_M$ – MS $_{P*M}$) / 73
σ^2_{P*M} = MS $_{P*M}$

For ECW: σ^2_P = (MS $_P$ – MS $_{P*M}$) / 2
σ^2_M = (MS $_M$ – MS $_{P*M}$) / 72
σ^2_{P*M} = MS $_{P*M}$.

SDD=smallest detectable difference, with two repeated measurements and a probability of 95%: SDD=$\sqrt{}$ MS $_{P*M}$ * $\sqrt{}$2 * 1.96.
For TBW: SDD=4.04, so with a probability of 95% score differences lie between – 3.3 and 4.8.
For ECW: SDD=3.55, so with a probability of 95% score differences lie between – 6.8 and 0.3.

Note: Limits of agreement are almost equivalent to SDD limits.
Factor 'patients' is considered to be a 'random' factor, the factor 'method' is fixed.

Table 3.5 Subcategory ICC values for measurement of TBW. Original ICC for all patients (n=73) is 0.943

Factors	ICC values for subcategories	
Gender	0.907 (males, n=41)	0.902 (females, n=32)
Cystic kidneys (PCKD)	0.886 (PCKD, n=9)	0.950 (non-PCKD, n=63)
Calcium antagonists	0.943 (users, n=27)	0.940 (non-users, n=45)

Covariates	Lowest 33% ICC	Middle 33% ICC	Highest 33% ICC
Age	0.980	0.967	0.915
BMI	0.924	0.949	0.933
Waist-to-hip ratio	0.919	0.939	0.912
Hydration status LBM	0.964	0.914	0.945
Ratio ECW to ICW	0.938	0.978	0.892
Creatinine clearance	0.948	0.906	0.959

ICC=intraclass correlation coefficient; TBW=total body water; PCKD=polycystic kidney disease; BMI=body mass index; LBM=lean body mass; ECW=extra-cellular water; ICW=intracellular water.

Extra-cellular water

Data of bromide dilution are available for 72 RTx patients (data of five patients were lost during laboratory analysis). Descriptive statistics of ECW measured by bromide dilution (ECW_{KBr}) and ECW measured by MF-BIA ($ECW_{MF\text{-}BIA}$) are shown in table 3.3. ECW_{KBr} compared with $ECW_{MF\text{-}BIA}$ is 15.5±2.9 liter *versus* 18.7±3.6 liter ($p<0.05$). ECW_{KBr} is highly and significantly correlated to $ECW_{MF\text{-}BIA}$ ($r=0.865$, $p<0.001$). The regression plot of ECW_{KBr} and $ECW_{MF\text{-}BIA}$ is given in figure 3.4. The Bland and Altman analysis is plotted in figure 3.5. The mean difference between ECW_{KBr} and $ECW_{MF\text{-}BIA}$ is 3.3 liter (95% CI: -3.7 to -2.8 liter). Limits of agreement show that $ECW_{MF\text{-}BIA}$ may be 0.4 liter lower or 6.9 liter higher than ECW_{KBr}.

The ICC for measurement of ECW by KBr dilution and MF-BIA (ICC_{ECW}) plus the way it is calculated is given in table 3.4. ICC_{ECW} turns out to be 0.846 (95% limits of agreement: -6.8 to 0.3 liter). This is below the predetermined acceptable method agreement. The approximate one-sided lower 95% confidence level for the ICC according to Fleiss[36] is 0.779. Subcategory ICC values are given in table 3.6. Many of the subcategories do not meet the lowest acceptable method agreement. Remarkably, method agreement appears to be acceptable in female patients, but not in male patients.

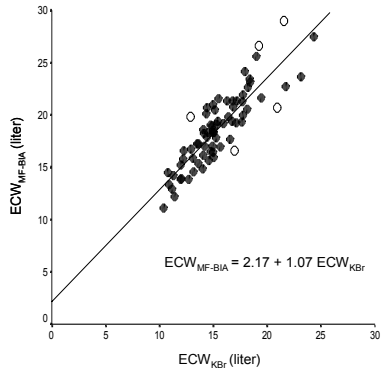


Figure 3.4 Regression plot of ECW_{KBr} and $ECW_{MF\text{-}BIA}$. Outliers (standardized z-residu scores <-2 or >2) are given as open circles.

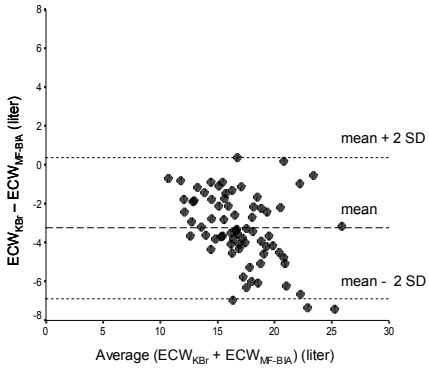


Figure 3.5 Assessment of ECW by KBr dilution against MF-BIA (Bland and Altman analysis) The relative bias (dilution minus MF-BIA) plotted against the size of the measurement (mean of dilution and MF-BIA).

Body fat and fat-free mass: MF-BIA compared to DEXA

For 75 RTx patients, DEXA total body scans are available. Descriptive statistics of body fat (BF, percentage of total body weight) measured by DEXA (BF_{DEXA}) and BF measured by MF-BIA ($BF_{MF\text{-}BIA}$) are shown in table 3.3. BF_{DEXA} compared with $BF_{MF\text{-}BIA}$ is 30.3±10.5% *versus* 33.7±9.2% ($p<0.05$). BF_{DEXA} and $BF_{MF\text{-}BIA}$ are highly and significantly correlated ($r=0.895$, $p<0.001$). The regression plot of BF_{DEXA} and $BF_{MF\text{-}BIA}$ is given in figure 3.6. In figure 3.7, the Bland and Altman analysis is plotted. The mean difference between BF_{DEXA} and $BF_{MF\text{-}BIA}$ is 3.4% (95% CI: -4.5 to -2.3%). Limits of agreement show that $BF_{MF\text{-}BIA}$ may be 6.0% lower or 12.8% higher than BF_{DEXA}.
The ICC for method agreement between BF_{DEXA} and $BF_{MF\text{-}BIA}$ ($ICC_{BF\text{-}D}$) is 0.887 (95% limits of agreement -12.6 to 5.8%). According to the Fleiss formula[36], the approximate one-sided 95% lower confidence level for the ICC turns out to be 0.836. The subcategory ICC values are shown in table 3.7. Method agreement appears to be acceptable in most of the subcategories. Especially in patients with cystic kidneys, in patients with a BMI<22.5 kg/m^2, and in patients with a high waist-to-hip ratio, method agreement appears to be below the predetermined lowest acceptable method agreement. Because FFM is calculated as 100% minus fat mass both in DEXA and in MF-BIA, the results of ICC and thus of method agreement with regard to FFM are identical.

Table 3.6 Subcategory ICC values for measurement of ECW. Original ICC for all patients (n=72) is 0.846

Factors	ICC values for subcategories	
Gender	0.817 (males, n=40)	0.877 (females, n=32)
Cystic kidneys (PCKD)	0.802 (PCKD, n=8)	0.841 (non-PCKD, n=63)
Calcium antagonists	0.853 (users, n=27)	0.845 (non-users, n=44)

Covariates	Lowest 33% ICC	Middle 33% ICC	Highest 33% ICC
Age	0.778	0.869	0.887
BMI	0.829	0.852	0.786
Waist-to-hip ratio	0.888	0.847	0.770
Hydration status LBM	0.875	0.816	0.875
Ratio ECW to ICW	0.871	0.916	0.857
Creatinine clearance	0.838	0.858	0.820

ICC=intraclass correlation coefficient; ECW=extra-cellular water; PCKD=polycystic kidney disease; BMI=body mass index; LBM=lean body mass; ICW=intracellular water.

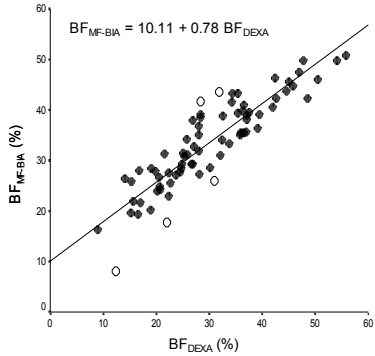


Figure 3.6 Regression plot of BF_{DEXA} and $BF_{MF\text{-}BIA}$. Outliers (standardized z-residu scores <-2 or >2) are given as open circles.

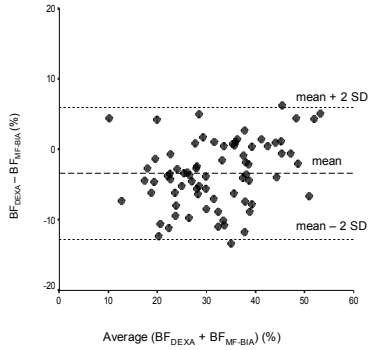


Figure 3.7 Assessment of BF by DEXA against MF-BIA (Bland and Altman analysis). The relative bias (DEXA minus MF-BIA) plotted against the size of the measurement (mean of DEXA and MF-BIA).

Table 3.7 Subcategory ICC values for measurement of percentage BF by DEXA and MF-BIA. Original ICC for all patients (n=75) is 0.887

Factors	ICC values for subcategories		
Gender	0.833 (males, n=41)	0.823 (females, n=34)	
Cystic kidneys (PCKD)	0.829 (PCKD, n=9)	0.889 (non-PCKD, n=65)	
Calcium antagonists	0.894 (users, n=27)	0.880 (non-users, n=47)	
Covariates	Lowest 33% ICC	Middle 33% ICC	Highest 33% ICC
Age	0.862	0.856	0.916
BMI	0.754	0.870	0.879
Waist-to-hip ratio	0.885	0.903	0.847
Hydration status LBM	0.865	0.915	0.919
Ratio ECW to ICW	0.919	0.831	0.896
Creatinine clearance	0.863	0.933	0.815

ICC=intraclass correlation coefficient; BF=body fat; DEXA=dual energy x-ray absorptiometry; MF-BIA=multi-frequency bio-electrical impedance analysis; PCKD=polycystic kidney disease; BMI=body mass index; LBM=lean body mass; ECW=extra-cellular water; ICW=intracellular water.

Body fat and fat-free mass: MF-BIA compared to anthropometry (skinfolds)

Anthropometric data are available for 74 RTx patients (in three patients it was not possible to measure skinfold thickness of the iliac crest because of multiple scars). Descriptive statistics of the percentage body fat measured by anthropometry (BF_{anthr}) and $BF_{MF\text{-}BIA}$ are shown in table 3.3. BF_{anthr} compared with $BF_{MF\text{-}BIA}$ is 27.9±10.2% *versus* 33.4±9.2% ($p<0.05$). BF_{anthr} is highly and significantly correlated to $BF_{MF\text{-}BIA}$ ($r=0.860$, $p<0.001$). The regression plot of BF_{anthr} and $BF_{MF\text{-}BIA}$ is given in figure 3.8. The Bland and Altman analysis is plotted in figure 3.9. The mean difference between BF_{anthr} and $BF_{MF\text{-}BIA}$ is 5.5±5.2% (95% CI: -6.7 to -4.3%). Limits of agreement show that $BF_{MF\text{-}BIA}$ may be 15.9% higher or 4.9% lower than BF_{anthr}.

The ICC for method agreement of BF by anthropometry and by MF-BIA ($ICC_{BF\text{-}A}$) is 0.856; because this ICC lies only a fraction above the predetermined lowest acceptable method agreement, method agreement between anthropometry and MF-BIA for measuring body fat appears to be questionable. The approximate one-sided lower 95% confidence level for the ICC turns out to be 0.793. Table 3.8 shows the subcategory ICC values. Also in most subcategories method agreement is poor. Because FFM is calculated as 100% minus fat mass both in anthropometry and in MF-BIA, the results of ICC and thus of method agreement with regard to FFM are identical.

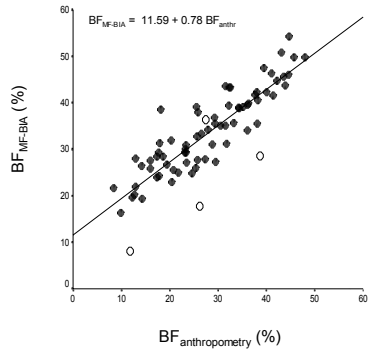


Figure 3.8 Regression plot of $BF_{anthropometry}$ and $BF_{MF\text{-}BIA}$. Outliers (standardized z-residu scores <-2 or >2) are given as open circles.

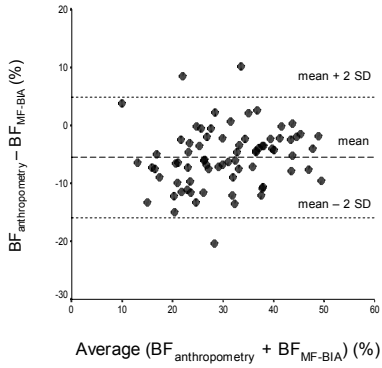


Figure 3.9 Assessment of BF by anthropometry against MF-BIA (Bland and Altman analysis). The relative bias (anthropometry minus MF-BIA) plotted against the size of the measurement (mean of anthropometry and MF-BIA).

Table 3.8 Subcategory ICC values for measurement of percentage BF by anthropometry (skinfolds) and MF-BIA. Original ICC for all patients (n=74) is 0.856

Factors	ICC values for subcategories		
Gender	0.722 (males, n=40)	0.827 (females, n=34)	
Cystic kidneys (PCKD)	0.884 (PCKD, n=9)	0.848 (non-PCKD, n=64)	
Calcium antagonists	0.834 (users, n=28)	0.866 (non-users, n=45)	
Covariates	Lowest 33% ICC	Middle 33% ICC	Highest 33% ICC
Age	0.735	0.857	0.897
BMI	0.602	0.859	0.897
Waist-to-hip ratio	0.899	0.856	0.773
Hydration status LBM	0.722	0.825	0.893
Ratio ECW to ICW	0.841	0.794	0.890
Creatinine clearance	0.784	0.910	0.776

ICC=intraclass correlation coefficient; BF=body fat; MF-BIA=multi-frequency bio-electrical impedance analysis; PCKD=polycystic kidney disease; BMI=body mass index; LBM=lean body mass; ECW=extra-cellular water; ICW=intracellular water.

Body fat and fat-free mass: DEXA compared to anthropometry (skinfolds)

DEXA total body scans and anthropometric data are available for 72 RTx patients. Descriptive statistics of BF_{DEXA} and BF_{anthr} are shown in table 3.3. BF_{DEXA} compared with BF_{anthr} is 30.2±10.7% *versus* 28.1±10.3% ($p<0.05$). BF_{DEXA} is highly and significantly correlated to BF_{anthr} ($r=0.913$, $p<0.001$). The regression plot of BF_{DEXA} and BF_{anthr} is given in figure 3.10. In figure 3.11, the Bland and Altman analysis is plotted. The mean difference between BF_{DEXA} and BF_{anthr} is 2.1% (95% CI: 1.1 to 3.1%); limits of agreement show that BF_{anthr} may be 6.7% higher or 10.9% lower than BF_{DEXA}.

The ICC for method agreement between BF_{DEXA} and BF_{anthr} ($ICC_{BF\text{-}DA}$) turns out to be 0.913 (95% limits of agreement: -6.5 to 10.7%). The approximate one-sided 95% lower confidence level for the ICC is 0.872. The subcategory ICC values are given in table 3.9. In most of the subcategories, the ICC is larger than 0.85; however, especially in patients with a BMI<22.5 kg/m^2, patients with a high waist-to-hip ratio, and patients with a low hydration status of the LBM, method agreement does not meet the predetermined acceptable level. The results of ICC and thus of method agreement with regard to FFM are identical.

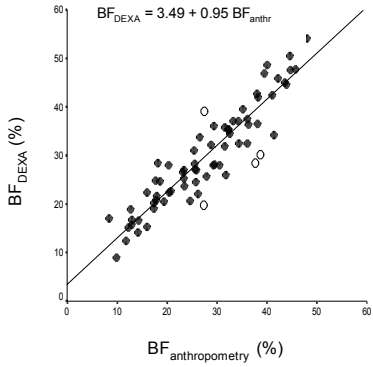


Figure 3.10 Regression plot of BF_{DEXA} and $BF_{anthropometry}$. Outliers (standardized z-residu scores <-2 or >2) are given as open circles.

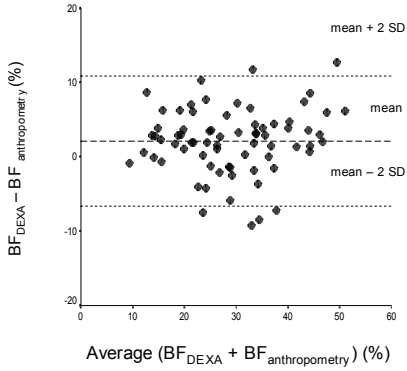


Figure 3.11 Assessment of BF by DEXA against anthropometry (Bland and Altman analysis). The relative bias (DEXA minus anthropometry) plotted against the size of the measurement (mean of DEXA and anthropometry).

Table 3.9 Subcategory ICC values for measurement of percentage BF by DEXA and anthropometry (skinfolds). Original ICC for all patients (n=72) is 0.913

Factors	ICC values for subcategories		
Gender	0.822 (males, n=39)	0.850 (females, n=33)	
Cystic kidneys (PCKD)	0.888 (PCKD, n=9)	0.912 (non-PCKD, n=62)	
Calcium antagonists	0.918 (users, n=27)	0.906 (non-users, n=44)	
Covariates	Lowest 33% ICC	Middle 33% ICC	Highest 33% ICC
Age	0.886	0.903	0.932
BMI	0.841	0.902	0.851
Waist-to-hip ratio	0.886	0.940	0.811
Hydration status LBM	0.806	0.943	0.925
Ratio ECW to ICW	0.947	0.842	0.931
Creatinine clearance	0.912	0.935	0.839

ICC=intraclass correlation coefficient; BF=body fat; DEXA=dual energy x-ray absorptiometry; PCKD=polycystic kidney disease; BMI=body mass index; LBM=lean body mass; ECW=extra-cellular water; ICW=intracellular water.

Discussion

In this study, we assessed in the first place the reproducibility of MF-BIA measurements, in the second place method agreement between MF-BIA and isotope dilution, DEXA, and anthropometry, and finally method agreement between DEXA and anthropometry in RTx patients.

Reproducibility of MF-BIA measurements

The reproducibility of the MF-BIA measurements was assessed by calculating coefficients of variation (CV) of duplicate measurements. The CV of the TBW measurements was 1.0%, and the CV of the ECW measurements was 0.6%. This suggests a high reproducibility of the TBW and ECW measurements by MF-BIA, as also reported by others[38-40].

Body water compartments: MF-BIA compared to isotope dilution

MF-BIA is based on the different conductive and dielectric properties of various biologic tissues at various frequencies of current. Blood, muscles, and other tissues that contain a lot of water and electrolytes are highly conductive; in contrast, bone, fat tissue, and air-filled spaces are highly resistive. Currents will flow predominantly through materials with higher conductivities[41]. The volume of the various tissues can be deduced from measurement of their resistances. In MF-BIA, the human body is considered as five conductive cylinders (i.e., the trunk, two arms, and two legs), which are connected in series. In conductors connected in series, the conductor with the smallest cross-sectional area (i.e.,

the arm) will determine most of the resistances in series. Although the trunk comprises nearly 50% of the total body weight, the trunk (conductor with the largest cross-sectional area) may have only little influence on the whole-body resistance[40,41].

MF-BIA measures body impedance at a wide range of frequencies. The advantage of MF-BIA above the classic single frequency bio-impedance measurements is the possibility of MF-BIA to discriminate between the extra-cellular and intracellular water compartment. At low frequencies, cell membranes act like a condenser and completely block the flow of the current through the intracellular pathway. At higher frequencies, the condenser function of the cell membranes is lost, and the current flows to both the extra- and intracellular compartments and thus to the total body water[30,31,42]. Another advantage of MF-BIA is that MF-BIA predicts the volume of TBW and ECW from a general mixture theory (theory of Hanai)[30-32]. Water compartments are directly calculated from resistance values, assuming specific resistances of ECW and ICW. So, empirically derived prediction formulas are no longer necessary for the estimation of TBW and ECW.

In this study, we validated MF-BIA against D_2O and KBr isotope dilution, a technique that is considered to be the gold standard for measurement of body water compartments in healthy subjects. The accuracy of isotope dilution for measurement of TBW is excellent; the accuracy is dependent on the uncertainty of the estimate of non-aqueous exchange, which is about 1%[20]. For TBW measurements by continuous flow isotope ratio mass spectrometry, used in this study, the accuracy is 1.6%[18]. The accuracy for the measurement of ECW by isotope dilution is about 5%[19].

Compared to D_2O dilution, MF-BIA underestimates TBW by 0.7±2.1 liter. ICC_{TBW} and the ICC values of the various subgroups are all >0.886. These high ICC values suggest good method agreement between D_2O dilution and MF-BIA for measuring TBW; therefore, for measuring TBW the D_2O dilution technique might be substituted by MF-BIA.

Dihydropyridine calcium antagonists, frequently prescribed for treatment of hypertension in RTx patients, can lead to peripheral edema. We investigated whether the use of these calcium antagonists influenced the reliability of MF-BIA; the ICC_{TBW} values in the group of patients using calcium antagonists and in the group of patients not using this medication are almost equal: 0.943 and 0.940, respectively. So, the use of calcium antagonists does not correlate with the method agreement for TBW.

We also investigated whether the presence of polycystic kidneys in the abdomen is related to method agreement. In patients with polycystic kidneys, the trunk contains a higher amount of body water than in patients without cystic kidneys. As mentioned earlier, in MF-BIA the trunk contributes hardly to the

whole-body resistance, which is a major parameter in the estimation of body water compartments by MF-BIA[40,41]. Therefore, in patients with polycystic kidney disease, MF-BIA might underestimate the TBW compared to isotope dilution, and method agreement might be lower. The ICC_{TBW} between isotope dilution and MF-BIA in patients without polycystic kidneys is excellent (0.950); in patients with cystic kidneys, the ICC_{TBW} appears to be somewhat lower, but still acceptable (0.886). So, the presence of cystic kidneys seems to be related to the method agreement between isotope dilution and MF-BIA for TBW.

Compared to KBr dilution, MF-BIA overestimates ECW by 3.3±1.8 liter. ICC_{ECW} is 0.846 and thus below the lowest acceptable method agreement. The ICC values in most of the subgroups of patients do not meet the acceptable level of method agreement either. The low method agreement in male patients (ICC_{ECW}=0.817) compared to the acceptable method agreement in female patients (ICC_{ECW}=0.877) is remarkable. An explanation for this acceptable method agreement in female transplant patients cannot be given as yet. So, in RTx patients method agreement for measuring ECW by KBr dilution and by MF-BIA is not acceptable; method agreement is only reached in some very specific subgroups of patients. However, these results should be interpreted with caution. As discussed before, TBW determination by MF-BIA is satisfactory. $TBW_{MF\text{-}BIA}$ is calculated as the sum of ECW and ICW. In contrast to the ICW, the ECW is measured directly by MF-BIA[33]. The excellent agreement between TBW_{D2O} and $TBW_{MF\text{-}BIA}$ suggests that some of the disagreement between ECW_{KBr} and $ECW_{MF\text{-}BIA}$ might be due to errors with the bromide dilution technique. Errors with the bromide isotope dilution technique might, especially in patients with an abnormal ECW, be due to the uncertainty in the correction constants for plasma water and Gibbs-Donnan equilibration as well as to penetration into the intracellular space due to changes in plasma protein concentrations and hematocrit[20].

Body fat: MF-BIA compared to DEXA

MF-BIA derives fat-free mass from the measured volume of TBW. Fat mass is calculated as body weight minus fat-free mass. In MF-BIA, it is assumed that fat is anhydrous and that the lean body mass contains a relatively constant proportion of water (73.2%), a proportion that is assumed to be true in healthy individuals[43]. A disturbed water status can significantly reduce the accuracy of predictions of fat-free mass and fat mass by MF-BIA. In RTx patients, the assumption of a constant hydration status is not invariably true.
As mentioned earlier, MF-BIA measures TBW with sufficient accuracy in RTx patients. The hydration status of the LBM (calculated as TBW_{D2O} divided by LBM_{DEXA}) in our study population is 0.709±0.04 l/kg LBM (range 0.596 to

0.836 l/kg LBM) and significantly different from the assumed hydration status. Therefore, MF-BIA probably overestimates the actual percentage of body fat.
We compared the values of $BF_{MF\text{-}BIA}$ to the values of BF_{DEXA}. DEXA is a very useful technique for directly assessing soft tissue as well as bone; it has been shown to be of relatively high accuracy and very high precision[26]. However, DEXA is not assumption-free: DEXA too assumes that the hydration status of the LBM is uniform and fixed at 0.732 l/kg LBM[26,27,44]. The degree to which DEXA measurements of soft tissue are sensitive to changes in hydration in adult humans remains unknown, and therfore further research is needed. Hence, DEXA cannot be considered as gold standard for measuring fat and fat-free mass at this moment.
Compared to DEXA, MF-BIA overestimates the percentage of body fat by 3.7±4.7%. The original ICC for method agreement between BF_{DEXA} and $BF_{MF\text{-}BIA}$ is 0.887. So, method agreement seems acceptable. However, when our RTx population is divided into males and females, method agreement is unacceptable in both groups; the reason for this is that given an equal patient-by-method error, the ICC is generally lower within relatively homogeneous subgroups. The ICC values in some other specific subcategories also do not meet the acceptable level of method agreement. An explanation for the low method agreement in these groups cannot be given as yet. So, in RTx patients, method agreement between DEXA and MF-BIA for measuring body fat is not acceptable; therefore, results of DEXA and MF-BIA fat-measurements may not be substituted for each other.

Body fat: MF-BIA compared to anthropometry

We also compared MF-BIA to anthropometry (skinfolds) for measuring body fat. Skinfold thickness measurements are rapid, simple, noninvasive, and inexpensive. In skinfold thickness measurements, it is assumed that the majority of body fat resides in subcutaneous regions, that there is a consistent relationship between subcutaneous and visceral fat, and that body fat distribution is stable[45,46,47]. It is also assumed that the density of the LBM is normal, i.e., that the hydration status of the LBM is normal (0.732 l/kg LBM) and that the bone mineral content represents a fixed fraction of the LBM[47,48]. The reliability of skinfold measurements is approximately 5%. It largely depends on the sites of the skinfold measurements and the experience of the examiner[45]. Anthropometric evaluation of body fat is most appropriate for population surveys. Skinfold measurements cannot be considered a gold standard for measurement of body fat content.
Compared to anthropometry, MF-BIA overestimates the percentage body fat in RTx patients by 5.5±5.2%. The original ICC for measurement of agreement between BF_{anthr} and $BF_{MF\text{-}BIA}$ is 0.856 and thus only a fraction above the lowest

acceptable level of method agreement. Therefore, method agreement seems to be questionable. Both in men and women the ICC for method agreement is unacceptable. In most of the other subgroups ICC values also indicate questionable, poor, or even very poor method agreement. The reason(s) for the low method agreement in these subgroups are not known.

Body fat: DEXA compared to anthropometry

At present, DEXA is used more and more for the measurement of total body fat content. However, as mentioned earlier, DEXA is not considered the gold standard for measurement of body fat. We finally compared DEXA to the relative simple anthropometric (skinfold thickness) measurements. Compared to DEXA, anthropometry underestimates the percentage of body fat in RTx patients by 2.1±4.4%. Hart et al.[49] also reported that skinfold measurements underestimate the percentage of body fat compared to DEXA in RTx patients. The original ICC for method agreement between DEXA and anthropometry found in our study is high, i.e., 0.913. So, method agreement seems to be very good. Nevertheless, there are a few subcategories of RTx patients in which the ICC is below the predetermined acceptable level and where method agreement thus is questionable. In patients with a low (<22.5 kg/m^2) and high (>26.0 kg/m^2) BMI, the poor method agreement can be explained by the fact that measurement of skinfolds in very lean and very obese subjects (who have respectively a low or high BMI) is technically difficult; therefore, the validity of skinfold measurements in these groups could be affected[50]. In patients with a high waist-to-hip ratio (apple configuration), the abnormal body fat distribution might play a role. Skinfold measurements, in which a stable body fat distribution is assumed, might be invalid in this patient group. In patients with a low hydration status (<0.6900 l/kg) method agreement is probably low because both anthropometry and DEXA assume a normal hydration status (0.732 l/kg LBM).

Method comparison for the measurement of fat-free mass

In MF-BIA and anthropometry (skinfold thickness measurements), the body is considered to be composed of two compartments: the fat compartment and the fat-free compartment (bone mass included)[41,47]. In DEXA, the body is divided into the fat compartment, the lean soft tissue compartment, and the bone mineral content (fat-free mass equals lean soft tissue mass plus bone mineral content)[27]. Thus, in MF-BIA as well as in DEXA and anthropometry, the percentage of fat-free mass equals 100% minus the percentage of body fat. Therefore, when the percentage of body fat is overestimated in the method comparisons, the percentage of fat-free mass will be underestimated, and conversely, when the percentage of body fat is underestimated, the percentage

of fat-free mass will be overestimated. Furthermore, the conclusions about the degree of method agreement between MF-BIA, DEXA, and anthropometry for the measurement of body fat are the same for the measurement of fat-free mass.

Conclusions

MF-BIA seems to be suitable to measure TBW with sufficient accuracy in RTx patients. The agreement between ECW_{KBr} and $ECW_{MF\text{-}BIA}$ is not satisfactory. However, possible limitations of the bromide isotope dilution technique have to be taken into account.

Because neither DEXA nor anthropometry can be considered a gold standard, the interpretation of the results of the method comparisons regarding fat and fat-free mass should be done with caution. Still, the poor agreement for measuring body fat and fat-free mass between MF-BIA and DEXA and between MF-BIA and anthropometry, and the reasonable agreement between DEXA and anthropometry, makes the reliability of MF-BIA in the assessment of fat and fat-free mass in RTx patients questionable.

References

1. Moore LW, Gaber AO. Patterns of early weight change after renal transplantation. J Ren Nutr 1996; 6:21-25.
2. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, Rocher LL, Campbell DA. Obesity and renal transplantation. Surg Gynecol Obstet 1991; 172:367-376.
3. Yanovski JA, Cutler CB. Glucocorticoid action and the clinical features of Cushing's syndrome. Endocrinol Metab Clin North Am 1994; 23:487-509.
4. Horber FF, Zuercher RM, Herren H, Crivelli MA, Robotti G, Frey FJ. Altered body fat distribution in patients with glucocorticoid treatment and in patients on long-term dialysis. Am J Clin Nutr 1986; 43:758-769.
5. Danovitch GM. Immunosuppressive medications and protocols for kidney transplantation, in Handbook of kidney transplantation. Danovitch GM, Editor. Little, Brown, and Compagny, Boston. 1992:67-104.
6. Chan MK, Varghese Z, Persaud JW, Fernando ON, Moorhead JF. The role of multiple pharmaco-therapy in the pathogenesis of hyperlipidemia after renal transplantation. Clin Nephrol 1981; 15:309-313.
7. Vathsala A, Weinberg RB, Schoenberg L, Grevel L, Dunn J, Goldstein RA, Van Buren CT, Lewis RM, Kahan BD. Lipid abnormalities in renal transplant recipients treated with cyclosporine. Transplant Proc 1989; 21:3670-3673.
8. Isoniemi H, Tikkanen M, Hayry P, Eklund B, Hockerstedt K, Salmela K, Ahonen J. Lipid profiles with triple drug immunosuppressive therapy and with double drug combinations after renal transplantation and stable graft function. Transplant Proc 1991; 23:1029-1031.
9. Lapidus L, Bengtsson C, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death; a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. BMJ 1984; 289:1257-1261.
10. Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death; 13 year follow up of participants in the study of men born in 1913. BMJ 1984; 288:1401-1404.
11. Gunnarsson R, Lofmark R, Nordlander R, Nyquist O, Groth CG. Acute myocard infarction in renal transplant recipients; incidence and prognosis. Eur Heart J 1984; 5:218.
12. Raine AEG, Margreiter R, Brunner FP, Ehrich JHH, Geerlings W, Landais P, Loirat C, Mallick NP, Selwood NH, Tufveson G. Report of managment of renal failure in Europe, XXII 1991. Nephrol Dial Transplant 1992; 7(Suppl 2):S7-35.
13. Hyperlipidemia after renal transplantation [Editorial]. Lancet 1988; 1(8591):919-920.
14. Markell MS, Friedman EA. Hyperlipidemia after organ transplantation. Am J Med 1989; 87(5N):61N-67N.
15. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7:158-165.
16. Ibels LS, Alfrey AC, Weil R. Hyperlipidemia in adult, pediatric and diabetic renal transplant recipients. Am J Med 1978; 64:634-642.
17. Bioelectrical impedance analysis in body composition measurement: National Institutes of Health Technology Assessment Conference Statement. Am J Clin Nutr 1996; 64 (Suppl 3):S524-532.
18. Van Kreel BK, Van der Vegt F, Meers M. Determination of total body water by a simple and rapid mass spectrometric method. J Mass Spectrom 1996; 31:108-111.
19. Van Kreel BK. An improved bromide assay for the estimation of extracellular water volume by capillary gas chromatography. Clin Chim Acta 1994; 231:117-128.
20. Schoeller DA. Hydrometry, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:25-44.
21. Schoeller DA, Van Santen E, Peterson DW, Dietz W, Jaspen J, Klein PD. Total body water measurements in humans with ^{18}O and ^{2}H labeled water. Am J Clin Nutr 1980; 33:2686-2693.
22. Edelman IS, Leibman J. Anatomy of body water and electrolytes. Am J Med 1959; 27: 256-277.

23. Donnan FG, Allmand AJ. Ionic equilibration across semi-permeable membranes. J Chem Soc 1914; 105:1941-1963.
24. Miller ME, Cosgriff JM, Forbes GB. Bromide space determination using anion-exchange chromatography for measurement of bromide. Am J Clin Nutr 1989; 50:168-171.
25. Bell EF, Ziegler EE, Forbes GB. Corrected bromide space. Pediatr Res 1984; 18:392-393.
26. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990; 51: 1106-1112.
27. Lohman TG. Dual energy x-ray absorptiometry, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:63-78.
28. Durnin JVGA, Womersly J. Body fat assessed from total body density and its estimation from skinfold thickness measurements in 481 men and women aged from 16 to 72 years. Br J Nutr 1974; 32:77-97.
29. Siri WE. The gross composition of the body. In: Advances in biological and medical physics. Tobias CA, Lawrence JH, Editors. Academic Press, New York. 1956:239-280.
30. Van Loan MD, Kopp LE, King JC, Wong WW, Mayclin PL. Fluid changes during pregnancy: use of bioimpedance spectroscopy. J Appl Physiol 1995; 78:1037-1042.
31. De Lorenzo A, Andreoli A, Matthie J, Withers P. Predicting body cell mass with bioimpedance by using theoretical methods: a technological review. J Appl Physiol 1997; 82:1542-1558.
32. Hanai T. Electrical properties of emulsions, in Emulsion Science. Sherman PH, Editor. Academic Press, London. 1968:354-377.
33. Operating manual Xitron 4000B: Bio-impedance spectrum analyser system. Xitron Technologies Inc., San Diego CA, USA.
34. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. Statistican 1983; 32:307-317.
35. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet 1986; 1:307-310.
36. Fleiss JL. The design and analysis of clinical experiments. John Wiley and Sons, New York. 1986:1-32.
37. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
38. Hannan WJ, Cowen SJ, Plester CE, Fearon KCH, DeBeau A. Comparison of bio-impedance spectroscopy and multi-frequency bio-impedance analysis for the assessment of extracellular and total body water in surgical patients. Clinical Science 1995; 89:651-658.
39. Van Marken Lichtenbelt WD, Westerterp KR, Wouters L, Luijendijk SCM. Validation of bioelectrical impedance measurements as a method to estimate body-water compartments. Am J Clin Nutr 1994; 60:159-166.
40. Van Loan MD, Withers P, Matthie J, Mayclin PL. Use of bio-impedance spectroscopy (BIS) to determine extracellular fluid (ECF), intracellular fluid (ICF), total body water (TBW) and fat free mass (FFM). In: Human body composition: in vivo methods, models and assessment. Ellis KJ, Eastman JD, Editors. Plenum, New York. 1993:67-70.
41. Baumgartner RN. Electrical impedance and total body electrical conductivity. In: Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:79-107.
42. Kushner RF. Bioelectrical impedance analysis: a review of principles and applications. J Am Col Nutr 1992; 11:199-209.
43. Pace N, Rathbun EN. Studies on body composition. III. The body water and chemically combined nitrogen content in relation to fat content. J Biol Chem 1945; 158:685-691.
44. Roubenoff R, Kehayias JJ, Dawson-Hughes B, Heymsfield SB. Use of dual-energy x-ray absorptiometry in body composition studies: not yet a ‘gold standard’. Am J Clin Nutr 1993; 58:589-591.
45. Lukaski HC. Methods for the assessment of human body composition: traditional and new. Am J Clin Nutr 1987; 46:537-556.
46. Jensen MD. Research techniques for body composition assessment. J Am Diet Assoc 1992; 92:454-460.

47. Roche AF. Anthropometry and ultrasound, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:167-190.
48. Going SB. Densitometry, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:3-24.
49. Hart PD, Wilkie ME, Edwards A, Cunningham J. Dual energy x-ray absorptiometry versus skinfold measurements in the assessment of total body fat in renal transplant recipients. Eur J Clin Nutr 1993; 47:347-352.
50. Gray DS, Bray GA, Gemayel N, Kaplan K. Skinfold thickness measurements in obese subjects. Am J Clin Nutr 1990; 51:571-577.

Chapter 4

Post-transplantation weight gain is predominantly due to an increase in body fat mass

ECH van den Ham, JP Kooman, MHL Christiaans, KML Leunissen, JP van Hooff

Transplantation 2000; 70:241-242

Abstract

Background
Body weight usually increases after renal transplantation. Studies towards changes in body composition after renal transplantation are however scarce. Aim of the study was to assess changes in body composition in renal transplant patients without episodes of acute rejection or intercurrent disease in the first six months after transplantation.

Patients and methods
Eleven renal transplant patients (nine males, two females) were studied. Immunosuppression consisted of prednisolone, tacrolimus, and mycophenolate mofetil. Body composition was assessed by dual energy x-ray absorptiometry (DEXA). The first DEXA measurement was performed 3-4 weeks after renal transplantation. Follow-up measurements were performed three and six months after transplantation.

Results
Body weight ($p<0.05$) and body fat mass ($p<0.05$) increased significantly in the first six months after renal transplantation. Fat mass in the trunk increased significantly ($p<0.01$), whereas changes in extremity fat mass did not reach statistical significance. No significant changes in lean body mass were observed during the follow-up period.

Conclusion
Weight gain in the first six months after renal transplantation is primarily due to an increase in body fat mass. Changes in truncal fat mass are most pronounced. This could have adverse effects on the lipid metabolism, insulin resistance, and atherogenesis in renal transplant patients.

Introduction

Malnutrition is common in hemodialysis patients and is strongly associated with increased morbidity and mortality. It is generally assumed that nutritional status improves after renal transplantation, because usually an increase in body weight is observed[1]. However, in cross-sectional studies, a relatively high fat mass was observed in renal transplant (RTx) patients[2], which could be of importance in view of the high prevalence of hyperlipidemia and atherosclerosis in this population. Still, few studies have addressed the exact change in body composition after renal transplantation in a prospective way[3,4]. Moreover, in the available studies, patients with acute rejection and severe intercurrent illness were not excluded, which might have had an independent influence on nutritional state. Therefore, we undertook a study in which the change in body composition in RTx patients without episodes of acute rejection or severe disease was assessed in the first six months after transplantation.

Patients and methods

Patients

Eleven RTx patients participating in a multi-center trial within the first six months after transplantation were included in this study. Age ranged from 46 to 64 years. All patients were in clinically stable condition. At the time of inclusion, they had not experienced episodes with acute rejection or intercurrent diseases. As a part of the multi-center study, patients received triple-drug immunosuppressive therapy: methylprednisolone 125 mg before and the day after transplantation, followed by 20 mg prednisolone daily, which was tapered to a maintenance dose of 10 mg during the first month. Moreover, mycophenolate mofetil (500 mg bid) and tacrolimus (plasma level 15-20 ng/ml during the first two weeks, 10-15 ng/ml from day 14 to day 30, and 7-10 ng/ml thereafter) were prescribed. The multi-center trial was completed six months after renal transplantation.

Written informed consent was obtained from each patient prior to participation. The study was approved by the Ethical Committee of the Maastricht University Hospital.

Methods

Body composition

Body composition was assessed by dual energy x-ray absorptiometry (DEXA; DPX-L, Lunar radiation Corp., Madison, WI)[5]. DEXA measures body

composition by emission of two distinct x-ray beams (38 and 70 KeV), which are attenuated by tissues to different extents. From these differences in attenuation, DEXA estimates lean body mass (LBM), fat mass (FM), and bone mineral content (BMC). The coefficient of variation of DEXA measurements is 1.1%. The first DEXA measurement (baseline) was performed 3-4 weeks after renal transplantation because at this point in time, all patients had adequate diuresis and were clinically euvolemic. The other measurements were performed three and six months after renal transplantation.

Renal function

The formula of Cockcroft and Gault[6] was used to estimate creatinine clearance in the RTx patients. Creatinine clearance was assessed three and six months after transplantation.

Statistics

Friedman's analysis of variance was used for statistical analysis. Data are expressed as mean±SD (median). Statistical analysis was performed using SPSS for windows, version 7.5. P-values <0.05 were considered to be statistically significant.

Results

Patients characteristics

Clinical characteristics of the patients are given in table 4.1. The mean age of the RTx patients (nine males, two females) was 57.9±5.0 years. Body weight and body mass index (BMI) at baseline were on average 77.4±13.2 kg and 25.7±5.0 kg/m^2, respectively. Mean creatinine clearance, assessed by the Cockcroft and Gault formula[6], was 60.4±11.7 ml/min (median 58.0 ml/min) at three months and 64.4±11.7 ml/min (median 62.0 ml/min) at six months ($p<0.05$). None of the patients experienced episodes of acute rejection or severe intercurrent diseases during the follow-up period.

Body composition

The changes in body composition in the first six months after renal transplantation are given in table 4.2. Body weight and body FM increased significantly in the first six months after transplantation ($p<0.05$), whereas LBM did not change significantly over this time period. Figure 4.1 shows the changes in total body, truncal, and extremity FM. FM in the truncal region

increased significantly (p<0.01). Extremity FM increased also, but this increase was just not statistically significant.

Table 4.1 Clinical characteristics of the RTx patients (n=11) at baseline

Characteristics	
Age (yr)	57.9 ± 5.0 (58.0)
Gender (M/F)	9 / 2
Body weight (kg)	77.4 ± 13.2 (72.2)
BMI (kg/m^2)	25.7 ± 5.0 (25.5)

Data given as mean ± SD (median); BMI=body mass index.

Table 4.2 Changes in body composition in the first six months after renal transplantation

	Baseline	Month 3	Month 6	p-value
Body weight (kg)	77.4 ± 13.2 (72.2)	78.9 ± 11.1 (74.1)	81.4 ± 9.9 (80.6)	0.02
Body FM (kg)	21.4 ± 9.7 (19.1)	22.8 ± 8.7 (22.2)	24.6 ± 8.8 (24.9)	0.03
FM extremities (kg)	8.6 ± 4.5 (7.2)	9.0 ± 4.0 (9.0)	9.8 ± 4.3 (10.3)	0.09
FM trunk (kg)	11.5 ± 4.8 (11.4)	12.5 ± 4.5 (12.2)	13.3 ± 4.3 (14.0)	0.006
LBM (kg)	52.8 ± 10.7 (52.9)	52.9 ± 10.4 (55.7)	53.6 ± 9.8 (54.8)	0.15

Data given as mean ± SD (median); FM=fat mass; LBM=lean body mass.

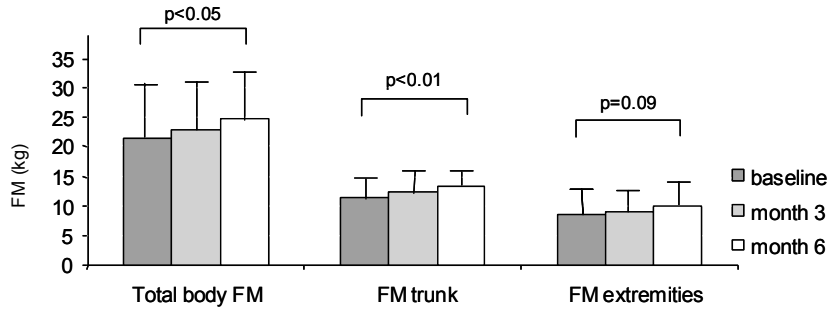


Figure 4.1 Changes in total body, truncal and extremity fat mass in the first six months after renal transplantation (n=11). FM=fat mass.

Discussion

In this prospective study, we observed that the post-transplant weight gain is - at least until six months after renal transplantation - predominantly due to an increase in FM. The increase in FM was already evident within three months after transplantation. Although also extremity FM increased, the changes in truncal FM were most pronounced. Body composition was assessed by DEXA.

Because hydration state may have an important effect on LBM, we chose to perform the baseline measurements three to four weeks after renal transplantation, when all patients were clinically euvolemic. The cause of the large increase in FM after renal transplantation remains to be elucidated. Corticosteroids may play an important role. In the study by Steiger et al.[3], daily prednisone doses were inversely related to lipid oxidation, suggesting that corticosteroids might affect body FM in a dose-dependent way. In addition, in a cross-sectional study in long-term RTx patients, we found an inverse relation between physical activity and FM[7]. It is therefore tempting to speculate that the combination of the increased dietary intake due to reversal of the uremic state, in combination with the use of corticosteroids and physical inactivity, leads to a predominant increase in body fat stores in the short term after transplantation.

Conclusion

The weight gain observed in the first months after renal transplantation is predominantly due to an increase in body FM, the changes in truncal FM being most pronounced. This could have adverse effects on the lipid metabolism, insulin resistance, and atherogenesis in RTx patients.

References

1. Miller DG, Levine SE, D'Elia JA, Bistrian BR. Nutritional status of diabetic and nondiabetic patients after renal transplantation. Am J Clin Nutr 1986; 44(1):66-69.
2. Qureshi AR, Lindholm B, Alvestrand A, Bergstrom J, Tollemar J, Hultman E, Groth CG. Nutritional status, muscle composition and plasma and muscle free amino acids in renal transplant patients. Clin Nephrol 1994; 42(4):237-245.
3. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger P, Horber FF. Body composition and fuel metabolism after kidney grafting. Eur J Clin Invest 1995; 25(11):809-816.
4. Isiklar I, Akin O, Demirag A, Niron EA. Effects of renal transplantation on body composition. Transplant Proc 1998; 30(3):831-832.
5. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry. J Am Soc Nephrol 1999; 10(5):1067-1079.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.
7. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation 2000; 69(8):1591-1598.

Chapter 5

The influence of early steroid withdrawal on body composition and bone mineral density in renal transplant patients

ECH van den Ham, JP Kooman, MHL Christiaans, JP van Hooff

Transplant International 2003; 16:82-87

Abstract

Background
Corticosteroid treatment may have an important effect on body composition and bone mineral density in renal transplant patients. We investigated the effect of early steroid withdrawal on body composition and bone mineral density in renal transplant patients in a prospective design.

Patients and methods
Post-transplant immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisolone. Three months after renal transplantation, 27 patients participating in a multi-center trial were randomized either to continue steroids (at a dose of 10 mg/day, n=17; steroid+) or be withdrawn from steroids within two weeks (n=10; steroid-). Body composition and bone mineral density (lumbar spine (L2-L4) and femoral neck) were measured by dual energy x-ray absorptiometry just before and three months after randomization.

Results
With regard to body composition, fat mass tended to increase in the steroid+ group (1.1±2.3 kg; p=0.084), but did not change in the steroid- group. Increase in body fat percentage tended to be higher (p=0.08) in the steroid+ group (0.6±2.7%) than in the steroid- group (-0.7±2.1%). The change in lean body mass was not significantly different between the two groups. Bone mineral density of the lumbar spine and femoral neck decreased significantly in the steroid+ group (-1.4±3.2% and -2.3±2.9% respectively, $p<0.05$), while no changes were observed in the steroid- group. The change in bone mineral density of the lumbar spine was significantly different between the steroid+ and the steroid- group, whereas the change in bone mineral density of the femoral neck was not significantly different.

Conclusions
The increase in fat mass tended to be higher in the group continuing on steroids, though not significant, due to large inter-individual variation. In general, the effect of early steroid withdrawal on body composition after renal transplantation appears to be modest. In addition, early steroid withdrawal seems to have beneficial effects on bone mineral density in renal transplant patients, especially in the lumbar region.

Introduction

Corticosteroids are an integral part of maintenance immunosuppressive therapy after renal transplantation. However, the long-term use of corticosteroids is associated with many adverse sequelae. Two major complications in renal transplant (RTx) patients, in which use of steroids has been implicated, are excessive weight gain and osteoporosis after transplantation. Whereas the health risks of osteoporosis are clear, excessive weight gain may also contribute to morbidity. In a previous study[1], we showed that early weight gain after renal transplantation was predominantly due to an increase in body fat mass (FM), which may represent a further risk factor for the persistently high cardiovascular morbidity in RTx patients.

With regard to the relation between bone disease and corticosteroids, there is general agreement that doses of prednisolone higher than 7.5 mg/day for longer than three months will result in bone loss in the vast majority of patients. However, it has never been investigated whether early withdrawal of corticosteroids has an important beneficial effect on bone loss after renal transplantation.

The influence of relatively low doses of steroids on body composition is less clear. Surprisingly, in a previous cross-sectional study, we did not find differences in body composition between RTx patients with maintenance steroid doses of 0 mg, 5 mg and 10 mg, whereas in a retrospective analysis no differences between RTx patients with these different steroid maintenance doses were observed in weight gain either, over a five-year period[2,3]. Nevertheless, higher steroid doses are generally used early after renal transplantation, which are likely to have an important effect on body composition. No previous study, however, has addressed the effect of early steroid withdrawal on body composition in RTx patients. With regard to these considerations, the aim of the study was to assess the effect of early steroid withdrawal on bone mineral density (BMD) and body composition in RTx patients early after transplantation.

Patients and methods

Patients

Forty-two patients participating in a multi-center trial within the first six months after renal transplantation were included. Exclusion criteria for the present study were episodes of acute rejection (greater than Banff II) or severe intercurrent diseases. Of the 42 patients, 15 experienced either severe infections or rejection and were not eligible for further study. Therefore, body composition was assessed in 27 RTx patients (21 males, 6 females). In four

patients (one male; three females), measurement of BMD was not possible for technical reasons. Patient characteristics are given in table 5.1. All patients had adequate diuresis and were clinically euvolemic. None of the patients received calcium, vitamin D, or bisphosphonate treatment.

As part of the multi-center trial, post-transplant immunosuppression consisted of tacrolimus (plasma level 15-20 ng/ml during the first two weeks, 10-15 ng/ml from day 14 to day 30, and 7-10 ng/ml thereafter), mycophenolate mofetil (MMF, 1000 mg/day), and prednisolone (20 mg/day from day two onward). On day 14, prednisolone dose was diminished to 15 mg/day and on day 28 to 10 mg/day. Three months after renal transplantation, patients were randomized to continue steroids (at a dose of 10 mg/day, n=17) or be withdrawn from steroids within two weeks (n=10). Eight of the 17 patients continuing steroids were randomized to stop having MMF three months after transplantation. The multi-center trial was completed six months after transplantation. After this period, steroids and/or MMF were tapered; tapering of steroids and/or MMF was, however, not performed in a standardized manner.

Clinical characteristics of the patients randomized to continue steroids (the steroid+ group) or be withdrawn from steroids (the steroid- group) are shown in table 5.1.

Table 5.1 Clinical characteristics of the RTx patients in the steroid+ group and steroid- group at time of randomization

		Steroid+ group (n=17)	Steroid+/MMF+ (n=9)	Steroid+/MMF- (n=8)	Steroid- group (n=10)
Age (yr)		52.4 ± 13.6 (57.5)	50.3 ± 17.2 (57.5)	54.8 ± 8.5 (55.7)	56.3 ± 17.2 (60.9)
Gender (M/F)		14 / 3	6 / 3	8 / 0	7 / 3
Creatinine clearance (ml/min)[a]		54.4 ± 12.8 (50.6)	54.9 ± 12.1 (55.3)	53.9 ± 14.4 (49.0)	63.1 ± 16.3 (64.7)
PTH (pmol/l)[b]		10.5 ± 7.8 (8.5)	13.5 ± 9.4 (10.2)	7.4 ± 4.7 (5.3)	9.4 ± 7.3 (6.8)
Albumin (g/l)[b]		40.7 ± 3.8 (41.1)	41.2 ± 2.9 (41.2)	40.0 ± 4.8 (39.8)	40.4 ± 3.3 (40.1)
Calcium (mmol/l)[b]		2.53 ± 0.1 (2.53)	2.52 ± 0.12 (2.52)	2.54 ± 0.13 (2.55)	2.58 ± 0.2 (2.53)
Body composition					
Body weight (kg)		71.9 ± 7.8 (69.6)	74.4 ± 8.4 (74.1)	69.1 ± 6.3 (69.1)	76.9 ± 13.6 (75.6)
BMI (kg/m^2)		24.2 ± 1.9 (24.1)	24.8 ± 2.3 (25.9)	23.5 ± 1.3 (23.1)	26.0 ± 4.0 (25.4)
FM (kg)		20.5 ± 6.5 (20.4)	23.3 ± 7.0 (22.0)	17.3 ± 4.3 (17.0)	23.1 ± 6.4 (23.1)
LBM (kg)		51.4 ± 8.6 (54.8)	51.1 ± 10.7 (54.8)	51.8 ± 6.3 (52.3)	53.8 ± 10.0 (53.3)
Body fat (%)		28.5 ± 8.9 (27.5)	31.6 ± 1.3 (28.7)	25.1 ± 5.8 (25.6)	30.0 ± 6.3 (30.4)
Bone mineral density					
Lumbar spine:	BMD (g/cm^2)	1.219 ± 0.19 (1.229)	1.217 ± 0.24 (1.229)	1.220 ± 00.9 (1.221)	1.165 ± 0.27 (1.210)
	T-score	0.1 ± 1.5 (-0.1)	-0.1 ± 1.9 (-0.9)	-0.1 ± 0.9 (-0.1)	-0.6 ± 2.3 (-0.3)
	Z-score	0.3 ± 1.2 (0.2)	0.4 ± 1.4 (0.2)	0.3 ± 0.9 (0.2)	-0.3 ± 2.2 (0.1)
Femoral neck:	BMD (g/cm^2)	0.865 ± 0.12 (0.857)	0.842 ± 0.14 (0.801)	0.899 ± 0.09 (0.870)	0.872 ± 0.19 (0.893)
	T-score	-1.5 ± 0.8 (-1.4)	-1.6 ± 0.9 (-2.0)	-1.2 ± 0.7 (-1.2)	-1.4 ± 1.5 (-1.4)
	Z-score	-0.6 ± 0.7 (-0.8)	-0.8 ± 0.7 (-1.1)	-0.4 ± 0.7 (-0.6)	-0.6 ± 1.5 (-0.5)

Data are given as mean ± SD (median); [a] assessed by Cockcroft formula; [b] routine laboratory assessment; MMF=mycophenolate mofetil; PTH=parathyroid hormone; BMI=body mass index; FM=fat mass; LBM=lean body mass; BMD=bone mineral density.

Methods

Body composition and BMD of the lumbar spine and femoral neck were measured by dual energy x-ray absorptiometry (DEXA) at the time of randomization (i.e., three months after transplantation) and six months after transplantation. The equipment used in this study was DPX-L (Lunar Radiation Corp., Madison, WI).
DEXA measurements were performed in a standard fashion while the patient was lying in a supine position on a table. From an x-ray source and K-edge filter below the patient, x-ray beams of stable energy radiation of 38 and 70 KeV were emitted. Attenuation of the x-rays was measured with a detector situated above the patient. Transverse scans of the body were made from top to toe. For each transverse scan, about 120 pixel elements with a size of approximately 5*10 mm yielded data on the attenuation ratio. Approximately 40 to 45% of the pixels over the body contain bone and soft tissue, 55 to 60% contain soft tissue alone[4]. Bone mass was estimated from the ratio of attenuation at low energy peaks relative to that at high energy peaks through bone-containing pixels after correction for the overlying soft tissue. The composition of soft tissue was estimated by the ratio of beam attenuation at lower energy relative to that at higher energy in soft tissue pixels; this ratio is inversely and linearly related to the fat percentage[4,5]. The coefficient of variation of DEXA measurements is 1.1%.

Statistics

Because of the small group of patients studied and the fact that assumptions of normal distribution of the variables were not met, non-parametric statistical tests were used for comparisons. The RTx patients with steroid immuno-suppression and the patients with steroid-free immunosuppression were compared for changes in body composition and BMD by means of Mann-Whitney *U* tests. Changes within the different groups were assessed with Wilcoxon signed rank tests. Data were expressed as mean±SD (median). Statistical analysis was performed by using SPSS for Windows, version 9.0.

Results

Clinical characteristics of the RTx patients at the time of randomization are given in table 5.1. Seventeen patients (14 males, 3 females) were randomized to continue steroids (the steroid+ group), whereas 10 patients (seven males, three females) were randomized to be withdrawn from steroids within two weeks (the steroid- group). At the time of randomization, the steroid+ and steroid- groups were comparable for age, creatinine clearance, and levels of

parathyroid hormone, albumin, and calcium. The steroid groups were also comparable for body composition, BMD of the lumbar spine, and BMD of the femoral neck. All patients included completed the study; none of them suffered periods of acute rejection or had serious abdominal complaints (i.e., pain, dyspepsia, or diarrhea) or intercurrent diseases during the study period.
Changes in body composition and BMD in the steroid+ and steroid- groups are given in table 5.2. Body weight increased significantly by 1.8±2.7 kg in the steroid+ group, while it did not change significantly in the steroid- group. FM tended to increase in the steroid+ group (1.1±2.3 kg, p=0.084), but did not change in the steroid- group. In both steroid groups, no changes in lean body mass (LBM) were observed. The body fat percentage in the steroid+ group did not change; in the steroid- group, however, the body fat percentage decreased significantly (-0.7±2.1 kg, p<0.05). Changes in body weight, FM, and LBM were not significantly different between the steroid+ and steroid- groups. In contrast, the change in body fat percentage tended to be different between the two steroid groups (p=0.08).

Table 5.2 Changes in body composition and BMD in RTx patients with and without steroids

	Steroid- group (n=10)	Steroid+ group (n=17)	Subgroup Steroid+/MMF+ (n=9)	Subgroup Steroid+/MMF- (n=8)
Body composition				
Δ body weight (kg)	0.7 ± 2.3	1.8 ± 2.7[a]	1.7 ± 3.7	1.8 ± 0.8[a]
Δ FM (kg)	-0.4 ± 1.4	1.1 ± 2.3	1.5 ± 2.9	0.7 ± 1.6
Δ LBM (kg)	1.0 ± 2.7	0.6 ± 2.3	0.2 ± 2.9	1.1 ± 1.5[a]
Δ body fat (%)	-0.7 ± 2.1[a]	0.6 ± 2.7	1.0 ± 3.1	0.3 ± 2.4
Bone mineral density				
Lumbar spine: Δ BMD (%)	1.9 ± 4.2[d]	-1.4 ± 3.2[a]	-1.6 ± 4.0	-1.1 ± 1.9
Δ T-score	0.1 ± 0.3[e]	-0.2 ± 0.3[b]	-0.2 ± 0.4	-0.2 ± 0.2
Δ Z-score	0.1 ± 0.2[d]	-0.3 ± 0.3[a]	-0.4 ± 0.4	-0.2 ± 0.3
Femoral neck: Δ BMD (%)	-0.3 ± 6.2	-2.3 ± 2.9[a]	-1.1 ± 3.0	-4.0 ± 1.8[af]
Δ T-score	0.0 ± 0.3	-0.2 ± 0.3[a]	-0.1 ± 0.2	-0.4 ± 0.2[af]
Δ Z-score	0.0 ± 0.4	-0.2 ± 0.2[c]	-0.1 ± 0.2	-0.4 ± 0.1[af]

Data are given as mean ± SD. Changes (i.e., Δ) are the mean of the individual changes in the period between three and six months after transplantation. [a] p<0.05 compared to time of randomization; [b] p=0.053 compared to time of randomization; [c] p<0.01 compared to time of randomization; [d] p<0.01 compared to steroid+ group; [e] p<0.05 compared to steroid+ group; [f] p<0.05 compared to steroid+/MMF+ group; MMF=mycophenolate mofetil; FM=fat mass; LBM= lean body mass; BMD=bone mineral density.

BMD and Z-score of the lumbar spine decreased significantly in the steroid+ group (-1.4±3.2% and -0.3±0.3, respectively, p-values both <0.05); the T-score of the lumbar spine tended to decrease (-0.2±0.3, p=0.053). This was in

contrast to the steroid- group, in which no significant changes in BMD, T-score and Z-score of the lumbar spine were observed. However, the change in BMD, T-score and Z-score of the lumbar spine was significantly different between the steroid groups.
Moreover, BMD, T-score and Z-score of the femoral neck decreased significantly in the steroid+ group (-2.3±2.9%, -0.2±0.3, and -0.2±0.2, respectively; $p<0.05$, $p<0.01$, and $p<0.05$, respectively). In the steroid- group no significant changes in BMD, T-score and Z-score of the femoral neck were observed. Changes in BMD, T-score and Z-score were not significantly different between the two steroid groups.

Discussion

In this prospective, randomized study, the increase in body fat percentage tended to be lower in patients with early steroid withdrawal than in patients continuing steroid immunosuppression, whereas the loss of vertebral bone mass was significantly higher in the patients continuing steroids than in the steroid-free group.

The effect of steroid treatment on FM could be explained by reduced lipolysis induced by corticosteroids. In acute hypercortisolemia, steroids acutely reduced lipolysis in subcutaneous fat[6], whereas in a study by Steiger et al.[7] in RTx patients, daily prednisone doses were inversely related to lipid oxidation. The present data are somewhat in contrast to our previous cross-sectional study, in which no difference in body composition was observed between RTx patients on maintenance steroid doses of 0 mg, 5 mg, and 10 mg, respectively; however, especially in female patients, a strong inverse relationship between physical activity level and FM was observed[2]. The difference between this previous study and the present one is that in the latter, the time of measurement was only between three and six months after transplantation. It can be hypothesized that early after transplantation, a period in which most patients are inactive, corticosteroids lead to an increase in FM which is maintained in patients with reduced physical activity. Later after renal transplantation, the effects of physical activity on body composition might become the predominant factor influencing body composition in RTx patients. The results of the present study with regard to body composition should, however, be interpreted with some caution because the differences did not formally reach significance due to wide variation. Moreover, DEXA cannot be considered a gold standard method, although at present it is assumed to be the most reliable method currently available to measure body composition in RTx patients[8,9].

With respect to BMD, the results are more straightforward. The decrease in BMD was significantly higher in patients on corticosteroid treatment than in the group receiving steroid-free immunosuppression. The effect was most pronounced in the vertebral region, which was to be expected, since trabecular bone in the cortical edge of the vertebrae is more susceptible to negative effects of corticosteroids than cortical bone from the hip[10,11,12]. Our data are in agreement with several previous studies that showed a significant relationship between steroid treatment and bone loss[12-15] and with the study by Aroldi et al.[16], in which lumbar BMD increased significantly in patients on cyclosporine mono-therapy and decreased significantly in patients receiving combined therapy with corticosteroids and cyclosporine. To our knowledge, the study by Aroldi et al.[16] and the present one are the only prospective data with regard to the effect of steroid withdrawal on BMD in RTx patients.
In the present study, BMD was assessed by DEXA. Although DEXA is as yet by far the most widely used technique for this purpose (despite ongoing discussion regarding the relation between DEXA measurements and fracture risk), it also cannot be considered a gold standard for the assessment of osteoporosis[17]. Vertebral height loss due to osteoporosis might give false elevated levels of BMD. In the present study, however, no significant height loss of the patients (which would give indirect evidence for vertebral height loss) was observed in the short follow-up period after renal transplantation. Moreover, hyperparathyroidism might also have an effect on the DEXA measurements[10,13,12]. However, no differences in parathyroid hormone or calcium levels were observed between patients in the steroid+ and steroid- group.

Several caveats from the present study should be mentioned. First, the patient group was rather small and the follow-up period rather short. However, it is likely that the effects on BMD and body composition are most pronounced especially early after renal transplantation when patients are treated with relatively high steroid doses. Second, patients were randomized to triple therapy, tacrolimus plus steroids or tacrolimus plus MMF (steroid-free). For reasons of power, the first two groups were combined. It is well-known that MMF frequently causes abdominal side effects such as pain, dyspepsia, and diarrhea. Therefore, the use of MMF might influence body composition. Indeed, some of the patients participating in the multi-center trial, receiving 1 g MMF/day, had serious abdominal complaints, possibly due to the use of MMF. These patients were however not included in the present study. Moreover, the changes in body composition between month 3 and month 6 after transplantation were not significantly different between the steroid+/MMF+ and steroid+/MMF- subgroups (table 5.2). Interestingly, BMD appeared to decrease to a larger degree in patients in the steroid+/MMF- group than in those in the

steroid+/MMF+ group (table 5.2). The reason for this is not clear and might be due to chance alone, as no theoretical background for a potential positive effect of MMF on BMD appears to be present. Therefore, although no study has yet investigated the effects of MMF on body composition or BMD, it is not likely that the combination of the steroid+/MMF+ and steroid+/MMF- subgroups into the steroid+ group will have had an important effect on the results of the study.

Conclusions

The increase in the body fat percentage in the early phase after renal transplantation tends to be higher in RTx patients randomized to continue steroids than in those randomized to be withdrawn from steroids. However, the effect of early steroid withdrawal on body composition after renal transplantation generally seems to be modest. Early steroid withdrawal appears to have beneficial effects on BMD in RTx patients, especially in the lumbar region.

References

1. van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP. Posttransplantation weight gain is predominantly due to an increase in body fat mass. Transplantation 2000; 70(1):241-242.
2. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation 2000; 69:1591-1598.
3. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Hooff JP. Weight changes after renal transplantation: a comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immunosuppressive therapy. Transplant Int 2003; 16:300-306.
4. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990; 51:1106-1112.
5. Lohman TG. Dual energy x-ray absorptiometry, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign (IL). 1996:63-78.
6. Samra JS, Clark ML, Humphreys SM, MacDonald IA, Bannister PA, Frayn KN. Effects of physiological hypercortisolemia on the regulation of lipolysis in subcutaneous adipose tissue. J Clin Endocrinol Metab 1998; 83(2):626-31.
7. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger Ph, Horber FF. Body composition and fuel metabolism after kidney grafting. Eur J Clin Invest 1995; 25:809-816.
8. Kerr PG, Strauss BJ, Atkins RC. Assessment of the nutritional state of dialysis patients. Blood Purif 1996; 14:382-387.
9. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual x-ray absorptiometry, and anthropometry. J Am Soc Nephrol 1999; 10:1067-1079.
10. Almond MK, Kwan JT, Evans K, Cunningham J. Loss of regional bone mineral density in the first 12 months following renal transplantation. Nephron 1994; 66:52-57.
11. Jehle PM, Jehle DR. Use of corticosteroids in nephrology - risk and prevention of osteoporosis induction. Nephrol Dial Transplant 2000; 15(5):565-568.
12. Smets YF, van der Pijl JW, de Fijter JW, Ringers J, Lemkes HH, Hamdy NA. Low bone mass and high incidence of fractures after successful simultaneous pancreas-kidney transplantation. Nephrol Dial Transplant 1998; 13:1250-1255.
13. Caglar M, Adeera L. Factors affecting bone mineral density in renal transplant patients. Ann Nucl Med 1999; 13:141-145.
14. Monier-Faugere MC, Mawad H, Qi Q, Friedler RM, Malluche HH. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. J Am Soc Nephrol 2000; 11(6):1093-1099.
15. Wolpaw T, Deal CL, Fleming-Brooks S, Bartucci MR, Schulak JA, Hricik DE. Factors influencing vertebral bone density after renal transplantation. Transplantation 1994; 58(11):1186-1189.
16. Aroldi A, Tarantino A, Montagnino G, Cesana B, Cocucci C, Ponticelli C. Effects of three immunosuppressive regimens on vertebral bone density in renal transplant recipients: a prospective study. Transplantation 1997; 63:380-386.
17. Grotz WH, Mundinger FA, Gugel B, Exner V, Kirste G, Schollmeyer PJ. Bone fracture and osteodensitometry with dual energy X-ray absorptiometry in kidney transplant recipients. Transplantation 1994; 58:912-915.

Chapter 6

Relation between steroid dose, body composition and physical activity in renal transplant patients

ECH van den Ham, JP Kooman, MHL Christiaans, JP van Hooff

Transplantation 2000; 69:1591-1598

Abstract

Background
Fat mass is increased in renal transplant patients, which may have untoward metabolic and cardiovascular effects. The influence of steroids on body composition, resting energy expenditure, and substrate oxidation rates was assessed in stable renal transplant patients in a cross-sectional design. Also, the relation between physical activity and nutrient intake, respectively, and body composition was studied.

Patients and methods
Seventy-seven renal transplant patients (42 males, 35 females) were studied. Twenty-one patients were on 10-mg and 27 patients on 5-mg maintenance steroid dose; twenty-nine patients were receiving steroid-free immunosuppression. Assessed were body composition (dual energy x-ray absorptiometry, anthropometry), resting energy expenditure and substrate oxidation rates (indirect calorimetry), physical activity (Baecke questionnaire) and nutrient intake (dietary records).

Results
Body composition was not different between the 0-mg, 5-mg and 10-mg steroid group, and no relationship existed between cumulative dose of steroids and body composition. Resting energy expenditure and substrate oxidation rates also did not differ between the various groups, apart from a small increase in glucose and decrease in lipid oxidation in female patients using 5 mg steroids. Especially in females, leisure time physical activity was positively related with the percentage lean body mass ($r=0.571$, $p=0.004$) and inversely related with fat mass ($r=-0.588$, $p=0.003$). Nutrient intake and body composition (corrected for physical activity) were not related.

Conclusions
No relation was observed between daily and cumulative steroid dosage and body composition, and between daily steroid dose and resting energy expenditure and substrate oxidation rates in renal transplant patients. Especially in female patients, physical activity level and the percentage of lean body mass and body fat were significantly related.

Introduction

Malnutrition is common in patients with end-stage renal failure and is strongly related to morbidity and mortality. Nutritional status may improve after renal transplantation. However, in the few studies that have addressed the impact of renal transplantation on body composition in more detail, especially an increase in body fat mass was observed[1-5]. This may have untoward effects on the lipid spectrum, glucose tolerance, and atherogenesis, which is especially important in relation to the increased cardiovascular mortality in renal transplant (RTx) patients[6-8]. Until now, the determinants of body composition in RTx patients have not been elucidated.

Steroid treatment may play a role in the disturbance of body composition in these patients. Glucocorticoids have profound effects on adipocytes, altering both lipid accumulation and mobilization; they usually cause weight gain and especially centripetal obesity (i.e., increased fat deposition in the peritoneum, mediastinum, and in subcutaneous sites on the face and the neck). Furthermore, glucocorticoid-treatment causes muscle wasting[9-11]. Steroid treatment could also possibly influence body composition by inducing changes in resting energy expenditure (REE) and substrate oxidation rates[2].

Physical activity may also have an influence on body composition. Physical activity plays a major role in preventing weight gain[12,13]. In general, by increasing the physical activity level, fat-free mass will increase and body fat mass will decrease[13-16]. In addition, in subjects who exercise regularly, less adipose tissue appears to accumulate in the upper, central body regions as they get older, and therefore the risk of metabolic disorders related to upper body fat accumulation potentially might be reduced[17]. Physical activity is decreased in dialysis patients[18,19], whereas little data exist on physical performance in RTx patients.

Another factor that may contribute to changes in body composition is the nutrient intake of the patients. After renal transplantation, the feeling of well-being, the disappearance of dietary restrictions, and also the increased appetite (the last probably due to steroid medication[10]), may result into an increased nutrient intake. A chronic increase of energy intake without an increase of energy expenditure will lead to weight gain.

In this cross-sectional study, we assessed the influence of steroids on body composition, REE, and substrate oxidation rates in stable RTx patients, including a group of patients on steroid-free immunosuppression. In addition, the influence of physical activity and nutrient intake on body composition was studied.

Patients and methods

Patients

Seventy-seven RTx patients (42 males, 35 females) participated in the study. Characteristics of the patients studied are shown in table 6.1. Only patients with a stable renal function and maintenance immunosuppressive therapy for at least two years were studied. Exclusion criteria were insulin-dependent diabetes mellitus, bone-prostheses, and recent complications (e.g., malignancies or surgery).

Table 6.1 Patient characteristics

	Total group (n=77)	Males (n=42)	Females (n=35)
Age (yr)	51.0 ± 11.7	49.6 ± 12.3	52.6 ± 10.9
Height (m)	1.68 ± 0.09	1.74 ± 0.06	1.61 ± 0.07[b]
Weight (kg)	69.6 ± 13.0	72.4 ± 12.1	66.2 ± 13.4[b]
% ideal body weight[a]	112.0 ± 19.6	108.2 ± 16.5	116.6 ± 22.2
Body mass index (kg/m^2)	24.8 ± 4.8	24.1 ± 4.1	25.7 ± 5.5
Follow-up after transplantation (yr)	9.1 ± 4.3	9.0 ± 4.0	9.2 ± 4.8
Cumulative dose of prednisolone (g)	19.3 ± 21.5	19.3 ± 20.4	19.3 ± 23.0
Serum creatinine (μmol/l)	139.1 ± 54.9	149.8 ± 55.0	126.3 ± 52.8

Data are given as mean ± SD; [a] percent ideal body weight was assessed on base of frame size (Metropolitan height and weight tables, American Life Assurance Compagny, 1983); frame size was determined by means of elbow breadth; [b] males versus females: $p<0.05$.

Twenty-one RTx patients (12 males, 9 females), transplanted in the pre-cyclosporine era, were using azathioprine and a maintenance prednisolone dose of 10 mg/day. Twenty-seven patients (15 males, 12 females) were treated with cyclosporine (in 12 patients combined with azathioprine) and a maintenance prednisolone dose of 5 mg/day. Twenty-nine patients (15 males, 14 females) were receiving cyclosporine mono-therapy without prednisolone; on the average, these patients were steroid-free for 7.0±3.3 years. Since the introduction of cyclosporine, the standard immunosuppressive regimen in our center consists of cyclosporine and low-dose prednisolone (10 mg/day) for recipients of first grafts. The prednisolone dose is diminished to 7.5 mg/day at month 1 and to 5 mg/day at month 3. In recipients without rejection, the prednisolone dose is further tapered to 0 mg in the next months. For highly immunized recipients (panel reactive antibodies >85%) and re-transplant recipients, azathioprine (±1 mg/kg body weight) is added to the above described regimen and the dose of prednisolone is tapered and maintained to 5 mg/day.

The clinical characteristics of the patients on 0-mg, 5-mg and 10-mg maintenance steroid therapy are given in table 6.2. The mean age of the

patients on steroid-free immunosuppressive therapy (55.8±11.4 years) was significantly higher compared with the age of the patients on 5 mg steroids (48.6±12.7 years) and 10 mg steroids (47.4±8.9 years). Follow-up after transplantation was significantly longer in the patients on 10 mg steroids (13.9±4.1 years) compared with patients on 5 mg (6.3±2.3 years) and 0 mg (8.1±3.0 years) steroids. Serum creatinine concentration in the 10-mg group was significantly lower than in the steroid-free group. Mean arterial pressure tended to be lower in the 10-mg group compared with the 5-mg and 0-mg group. Groups were comparable for height, weight, percentage of ideal body weight, body mass index (BMI), lipid profile, percentage of patients using β-blockers, the number of antihypertensive drugs used by the patients, and the percentage of patients using lipid lowering drugs. Moreover, the 0-mg and 5-mg group were comparable for daily dose of cyclosporine (mg per kg body weight) and 12-hr cyclosporine trough levels.
Informed consent was obtained from each patient and the study was approved by the Ethics Committee of the Maastricht University Hospital.

Table 6.2 Characteristics of the RTx patients on different maintenance steroid dosages

	0 mg steroids (n=29)	5 mg steroids (n=27)	10 mg steroids (n=21)
Age (yr)	55.8 ± 11.4[ef]	48.6 ± 12.7	47.4 ± 8.9
Gender (M/F)	15 / 14	15 / 12	12 / 9
Height (m)	1.68 ± 0.09	1.68 ± 0.08	1.68 ± 0.10
Weight (kg)	68.4 ± 11.5	70.8 ± 12.2	69.7 ± 16.1
% ideal body weight[a]	110.8 ± 18.8	113.4 ± 18.7	11.8 ± 22.5
Body mass index (kg/m^2)	24.5 ± 4.7	25.3 ± 4.5	24.7 ± 5.5
Follow-up after transplantation(yr)	8.1 ± 3.0[f]	6.3 ± 2.3[g]	13.9 ± 4.1
Cumulative dose of prednisolone (g)	2.2 ± 2.4[ef]	14.4 ± 6.9[g]	49.3 ± 16.6
Period steroid free (yr)	7.0 ± 3.3	-	-
Daily dose of cyclosporine (mg/kg body weight)	3.2 ± 1.0	3.3 ± 0.9	-
12-hr cyclosporine trough level (mg/l)	0.13 ± 0.04	0.11 ± 0.03	-
Serum creatinine (μmol/l)	156.4 ± 55.6[f]	140.1 ± 57.7	114.0 ± 41.3
Mean arterial pressure (mmHg)	95.1 ± 9.6	95.9 ± 7.2	89.3 ± 10.8
β-blockers (%)[b]	41	48	48
Antihypertensive drugs (number)[c]	1.3 ± 1.0	1.6 ± 0.9	1.4 ± 1.2
Total cholesterol (mmol/l)	5.6 ± 0.9	5.9 ± 1.2	5.7 ± 0.8
HDL-cholesterol (mmol/l)	1.3 ± 0.8	1.5 ± 0.6	1.5 ± 0.5
LDL-cholesterol (mmol/l)	3.5 ± 1.0	3.9 ± 1.1	3.5 ± 1.0
Triglycerides (mmol/l)	2.0 ± 0.9	1.9 ± 1.0	1.8 ± 0.9
Lipid lowering drugs (%)[d]	35	56	42

Data are given as mean ± SD; [a] % ideal body weight was assessed on base of frame size (Metropolitan height and weight tables, American Life Assurance; Compagny 1983); frame size was determined by means of elbow breadth; [b] percentage of patients using β-blockers; [c] mean number of antihypertensive drugs used by the patients; [d] percentage of patients using lipid lowering drugs; [e] group 0 mg steroids versus group 5 mg steroids: $p<0.05$; [f] group 0 mg steroids versus group 10 mg steroids: $p<0.05$; [g] group 5 mg steroids versus group 10 mg steroids: $p<0.05$; HDL=high density lipoprotein; LDL=low density lipoprotein.

Methods

In this cross-sectional study, the influence of steroids on body composition was assessed in two ways. First, the relationship between cumulative dose of steroids and body composition parameters was studied. We also compared the patient groups on maintenance steroid dosages of 0 mg, 5 mg and 10 mg/day for body composition parameters. Because of the well-known differences in body composition between males and females, separate analyses were performed for male and female RTx patients also.
Body composition of the patients was measured by dual energy x-ray absorptiometry (DEXA) and anthropometry. Indirect calorimetry was used to determine REE and substrate oxidation rates. Physical activity was assessed by means of the Baecke questionnaire. Nutrient intake was estimated by means of a dietary record.

Dual energy x-ray absorptiometry

DEXA was used to measure whole-body composition, i.e., fat mass (FM), lean soft tissue mass (comprising muscle, inner organs, and body water), and bone mineral content. Lean body mass (LBM) was calculated as lean soft tissue mass plus bone mineral content. Whole-body measurements were divided into areas of arms, legs, trunk, head and neck by the DEXA software. Body fat distribution was calculated by dividing upper-body FM (truncal FM) by lower-body FM (FM legs). The equipment used in this study was DPX-L (Lunar Radiation Corp., Madison, WI).

Anthropometry

Body weight was measured to the nearest 0.1 kg by using a balance scale. Body height was measured to the nearest 0.5 cm with the patient standing, back to a stadiometer. Body mass index (BMI) was calculated as body weight (kg) divided by body height (m) squared.
Skinfold measurements were used to estimate total body FM. Measurements were taken by a Harpenden skinfold caliper at the nondominant side of the body at four sites: biceps, triceps, subscapula, and iliac crest. Skinfolds were measured three times; thereafter, the sum of the individual skinfolds was averaged. The logarithm of the sum of the four skinfolds was used in age- and gender-specific regression equations of Durnin and Womersly[20] to compute body density (D). FM was computed as body weight (kg) * ((4.95/D) - 4.5), fat-free mass (kg) as body weight (kg) – FM (kg)[20,21].
Mid-upper arm circumference (MAC) was measured at the midpoint between the acromion and olecranon processes of the scapula and the ulna, respectively. MAC was used to calculate mid-arm muscle area (MMA) as follows: MMA (cm^2) = (MAC - (triceps skinfold * π))^2 / 4π. MMA was corrected for the mid-arm bone area by subtracting 10 cm^2 from the MMA in males, and

6.5 cm^2 from the MMA in females. MMA was used to estimate skeletal muscle mass.
Waist circumference was measured midway between the lower rib margin (costal margin) and the superior anterior iliac spine (iliac crest). Hip circumference was measured at the level of the great trochanters. Circumferences were measured to the nearest millimeter with a flexible tape, with the patient in standing position.

Indirect calorimetry

Oxygen uptake (VO_2) and carbon dioxide production (VCO_2) were measured by indirect calorimetry. The equipment used in this study was the Oxyconbeta (Mijnhardt b.v., Bunnik, The Netherlands). Measurements were performed after an overnight fast, in the morning. Smoking and physical activity were not allowed before the measurements. Mean values of VO_2 and VCO_2 (ml/min) were obtained over 15-20 minutes after reaching gas exchange steady state. Urinary nitrogen excretion (N_{urine}) was measured over 24 hr preceding the indirect calorimetry measurement. REE, glucose oxidation rate (GOX), lipid oxidation rate (LOX), and protein oxidation rate (POX) were calculated as follows[22,23]:

$$\text{REE (kcal/24 hr)} = ((3.94 * VO_2) + (1.10 * VCO_2) - (2.17 * N_{urine})) * 1440$$
$$\text{GOX (g/24 hr)} = ((4.55 * VCO_2) - (3.21 * VO_2) - (2.87 * N_{urine})) * 1440$$
$$\text{LOX (g/24 hr)} = ((1.67 * VO_2) - (1.67 * VCO_2) - (1.92 * N_{urine})) * 1440$$
$$\text{POX (g/24 hr)} = ((6.25 * N_{urine})) * 1440$$

REE, GOX, LOX, and POX are expressed relative to the LBM.

Baecke questionnaire

The Baecke questionnaire[24] was used for the measurement of habitual physical activity in RTx patients. This short questionnaire consisted of 16 items concerning occupation (eight items), sport (four items), and leisure time activities excluding sport (four items). All responses were precoded on a five-point Likert scale, ranging from never to always or very often, except the questions on the main occupation and the types of sport played. Occupational physical activity level was defined as low (housework, shopkeeping, clerical work, driving, teaching, studying, and all occupations with a university education), middle (factory work, plumbing, carpentry, and farming), or high (sport, dock work, and construction work). Sport physical activity level was classified as low, middle, and high depending on the average energy expenditure per hour. The sport score was calculated from the intensity of the

sport, time per week spent to play sport, and the proportion of the year the sport is performed.
The scores on the occupational, sport, and leisure time items were used to calculate the occupational activity index (OAI), sport activity index (SAI), and leisure activity index (LAI), respectively.

Nutrient intake

All patients were eating an ad libitum diet. The mean daily intake of total energy, carbohydrates, protein, and fat was evaluated by means of a three-day food record. Patients wrote down everything eaten during two weekdays and one weekend day. Before keeping their food record, patients were instructed on how to approximate food portion sizes and servings of fluid to ensure accurate reporting. Calculation of the nutrient intake was completed with a computerized nutrient analysis program.

Statistics

Values were expressed as mean±SD. Between-sex comparisons for descriptive variables were performed by using unpaired *t* tests for equal or unequal variances. Comparisons for descriptive variables and parameters of body composition, physical activity, nutrient intake, REE, and substrate oxidation rates between the RTx patients on maintenance dosages of prednisolone of 0 mg, 5 mg and 10 mg/day were performed by using one-way analysis of variance and post hoc Bonferroni tests. Relations between body composition and, respectively, cumulative prednisolone dose, physical activity, and nutrient intake and between steroid use and REE and substrate oxidation rates were studied by Pearson correlation coefficients. Multiple regression analysis was used to study the influence of various variables on body composition. P-values <0.05 were considered significant. All statistical analyses were performed using SPSS for windows, version 7.5.

Results

Body composition measurements by DEXA were performed in 75 patients (97.4% of the study population; 41 males, 34 females). Because of multiple scars in three of the patients, body composition by anthropometry was assessed in 74 patients (96.1% of the study population; 40 males, 34 females). Fifty-two patients (67.5% of the study population; 28 males, 24 females) completed the Baecke questionnaire on physical activity. Fifty-five patients (71.4% of the study population; 30 males and 25 females) reported their daily nutrient intake by means of a three-day food record. Sixty-six patients (85.7%

of the study population; 34 males and 32 females) collected urine for 24 hr, which was used to calculate REE.

Steroid use and body composition

Body composition and body fat distribution parameters of the male patients were significantly different compared to the parameters of the female patients, with the exception of BMI (table 6.3). Both the DEXA and anthropometric data showed less body fat and more LBM in men compared to women. The ratio of truncal FM and FM in the legs and the waist-to-hip ratio, however, were higher in male patients.

Table 6.3 Body composition, body fat distribution, REE and substrate oxidation rates, physical activity, and nutrient intake in RTx patients

	Total group (n=77)	Males (n=42)	Females (n=35)
Body weight (kg)	69.6 ± 13.0	72.4 ± 12.1[a]	66.2 ± 13.4
BMI (kg/m^2)	24.8 ± 4.8	24.1 ± 4.1	25.7 ± 5.5
DEXA			
FM (kg)	21.7 ± 9.9	17.9 ± 7.5[b]	26.2 ± 10.6
LBM (kg)	48.2 ± 9.3	54.4 ± 7.2[b]	40.7 ± 5.2
% body fat	30.3 ± 10.5	24.0 ± 7.1[b]	37.9 ± 8.9
% LBM	69.7 ± 10.5	76.0 ± 7.1[b]	62.1 ± 8.9
Ratio of truncal FM and FM legs	1.69 ± 0.47	1.82 ± 0.39[b]	1.52 ± 0.51
Anthropometry			
% body fat (skinfolds)	27.9 ± 10.2	21.6 ± 7.4[b]	35.4 ± 7.6
% LBM (skinfolds)	72.1 ± 10.2	78.4 ± 7.4[b]	64.6 ± 7.6
MMA (cm^2)	35.4 ± 8.0	38.0 ± 7.9[b]	32.4 ± 7.1
Waist-to-hip ratio	0.88 ± 0.08	0.92 ± 0.07[b]	0.82 ± 0.07
REE and substrate oxidation rates / 24 hr			
REE (kcal/kg LBM)	33.5 ± 3.7	31.7 ± 2.5[b]	35.5 ± 3.7
GOX (g/kg LBM)	3.5 ± 1.8	3.5 ± 1.8	3.6 ± 1.9
LOX (g/kg LBM)	1.5 ± 0.8	1.4 ± 0.8	1.6 ± 0.7
POX (g/kg LBM)	1.3 ± 0.4	1.2 ± 0.3[b]	1.5 ± 0.5
Physical activity			
OAI	2.68 ± 0.52	2.53 ± 0.56[a]	2.87 ± 0.40
LAI	2.69 ± 0.71	2.67 ± 0.77	2.72 ± 0.64
SAI	2.06 ± 0.93	2.03 ± 0.90	2.10 ± 0.98
Nutrient intake			
Energy intake (kcal/24 hr)	2033.7 ± 533.4	2274.6 ± 515.6[b]	1744.7 ± 399.4
Energy % carbohydrates	46.5 ± 7.4	46.3 ± 7.8	46.9 ± 7.1
Energy % protein	15.3 ± 3.3	14.5 ± 2.7[a]	16.4 ± 3.6
Energy % fat	35.3 ± 6.9	36.1 ± 7.4	34.5 ± 6.3

Data are given as mean ± SD; [a] $p<0.05$ compared to females; [b] $p<0.01$ compared to females; BMI= body mass index; DEXA=dual energy x-ray absorptiometry; FM=fat mass; LBM=lean body mass; MMA=mid-arm muscle area; REE=resting energy expenditure; GOX=glucose oxidation rate; LOX=lipid oxidation rate; POX=protein oxidation rate; OAI=occupational activity index; LAI=leisure time activity index; SAI=sport activity index.

The overall groups on 0-mg, 5-mg, and 10-mg maintenance steroid dose were not significantly different for body weight, total body FM, LBM, MMA, ratio of truncal FM and FM in the legs, and waist-to-hip ratio (table 6.4), nor did a significant relationship between each of these variables and the cumulative steroid dose exist.

Table 6.4 Body composition, body fat distribution, REE and substrate oxidation rates, physical activity, and nutrient intake in RTx patients on different maintenance steroid dosages

	0 mg steroids (n=29)	5 mg steroids (n=27)	10 mg steroids (n=21)
Body weight (kg)	68.4 ± 11.5	70.8 ± 12.2	69.7 ± 16.1
BMI (kg/m^2)	24.5 ± 4.7	25.3 ± 4.5	24.7 ± 5.5
DEXA			
FM (kg)	21.6 ± 9.9	22.5 ± 10.1	20.7 ± 10.2
LBM (kg)	46.6 ± 9.0	48.3 ± 8.5	50.3 ± 10.8
% body fat	31.0 ± 11.2	31.0 ± 11.0	28.4 ± 9.1
% LBM	69.0 ± 11.3	69.0 ± 11.0	71.6 ± 9.1
Ratio of truncal FM and FM legs	1.68 ± 0.40	1.63 ± 0.41	1.79 ± 0.63
Anthropometry			
% body fat (skinfolds)	28.9 ± 10.9	27.5 ± 10.5	27.1 ± 8.8
% LBM (skinfolds)	71.1 ± 10.9	72.5 ± 10.5	72.9 ± 8.8
MMA (cm^2)	36.3 ± 9.1	36.1 ± 6.8	33.4 ± 7.9
Waist-to-hip ratio	0.87 ± 0.08	0.87 ± 0.09	0.89 ± 0.10
REE and substrate oxidation rates / 24 hr			
REE (kcal/kg LBM)	33.4 ± 3.8	34.7 ± 3.7	32.0 ± 3.5
GOX (g/kg LBM)	2.94 ± 1.68[a]	4.24 ± 2.18	3.43 ± 1.18
LOX (g/kg LBM)	1.74 ± 0.75	1.35 ± 0.86	1.34 ± 0.62
POX (g/kg LBM)	1.28 ± 0.47	1.33 ± 0.36	1.47 ± 0.42
Physical activity			
OAI	2.56 ± 0.54	2.88 ± 0.43	2.64 ± 0.53
LAI	2.44 ± 0.61[b]	2.66 ± 0.70	3.02 ± 0.73
SAI	1.86 ± 0.82	2.12 ± 1.03	2.25 ± 0.96
Nutrient intake			
Energy intake (kcal/24 hr)	1978.9 ± 414.2	2030.6 ± 658.6	2110.6 ± 578.2
Energy % carbohydrates	47.0 ± 7.2	47.7 ± 5.5	44.9 ± 9.1
Energy % protein	15.6 ± 3.1	15.4 ± 3.7	14.9 ± 3.3
Energy % fat	35.5 ± 7.3	35.6 ± 6.9	34.9 ± 6.8

Data are given as mean ± SD; [a] group 0 mg steroids versus group 5 mg steroids: $p<0.05$; [b] group 0 mg steroids versus group 10 mg steroids: $p<0.05$; BMI=body mass index; DEXA=dual energy x-ray absorptiometry; FM=fat mass; LBM=lean body mass; MMA=mid-arm muscle area; REE=resting energy expenditure; GOX=glucose oxidation rate; LOX=lipid oxidation rate; POX=protein oxidation rate; OAI=occupational activity index; LAI=leisure time activity index; SAI=sport activity index.

When males and females were analyzed separately, both in males and females all body composition and body fat distribution parameters were not significantly different between patients on 0-mg, 5-mg, and 10-mg maintenance steroid therapy. In male patients, a weak, positive relation was found between the ratio

of truncal FM and FM in the legs and the cumulative dose of steroids (r=0.288, p=0.067), although it did not reach statistical significance. In female transplant patients, there was a trend for a decreased MMA with an increasing cumulative steroid dose (r=-0.325, p=0.057). Other body composition and body fat distribution parameters in males and females were not significantly related to the cumulative dose of steroids.

Steroid use and REE and substrate oxidation rates

REE and substrate oxidation rates of the patients are shown in table 6.3. REE and protein oxidation (POX) were significantly higher in female patients than in male patients. Males and females were comparable for glucose oxidation (GOX) and lipid oxidation (LOX).
The overall groups on 0-mg, 5-mg and 10-mg maintenance steroid dose were not significantly different for REE, LOX, and POX (table 6.4). Patients on a maintenance dose of 5 mg steroids had a significant higher GOX than patients on steroid-free maintenance immunosuppressive therapy. In male patients, REE, GOX, LOX, and POX were not significantly different between patients on 0-mg, 5-mg, and 10-mg maintenance steroid therapy. In females, the REE and POX were not significantly different between patients on 0-mg, 5-mg, and 10-mg steroid maintenance therapy. The GOX in patients on 5 mg steroids (5.04±2.06 g/kg LBM per 24 hr) was significantly higher compared to patients on 0 mg (2.57±1.35 g/kg LBM per 24 hr) and 10 mg steroids (2.92±0.88 g/kg LBM per 24 hr). The LOX of patients on 5 mg (1.19±0.85 g/kg LBM per 24 hr) was significantly lower compared to patients on steroid-free immuno-suppressive therapy (1.97±0.54 g/kg LBM per 24 hr).

Physical activity and body composition

The physical activity indices occupational activity index (OAI), leisure time activity index (LAI), and sport activity index (SAI) of the RTx patients are presented in table 6.3. The OAI in males was significantly lower compared to the OAI in females. The LAI and SAI of male and female patients were comparable.
In the overall group of patients, the OAI was inversely related to body weight (r=-0.277, p=0.047), LBM (r=-0.348, p=0.013), and to the waist-to-hip ratio (r=-0.382, p=0.005). No relationship was observed between the OAI and the other body composition and body fat distribution parameters. In males, a trend for a lower percentage of body fat (r=-0.360, p=0.065) and higher percentage of LBM (r=0.360, p=0.065) (both measured by anthropometry) with an increasing OAI was observed; percentage of body fat and LBM measured by DEXA, however, were not significantly related to the OAI. The OAI of males was not related to other parameters of body composition and body fat

distribution. In females, relations between the OAI and body composition and body fat distribution parameters were not observed either.
The LAI of the overall group of RTx patients was inversely related to BMI (r=-0.310, p=0.025) and to FM (r=-0.288, p=0.043). Other parameters of body composition and body fat distribution were not related to the LAI. In male patients, no relations were found between the LAI and body composition and body fat distribution. However, in females the LAI was inversely related to body weight (r=-0.523, p=0.009), BMI (r=-0.641, p=0.001), FM (r=-0.588, p=0.003), and percentage of body fat measured by DEXA and anthropometry (r=-0.567 and r=-0.572, respectively; p=0.005 and p=0.004 respectively); positive relations were observed between the LAI and the percentage of LBM measured by DEXA and anthropometry (r=0.571 and r=0.572, respectively, p=0.004). LAI was not related to other body composition and body fat distribution parameters in female patients.
The SAI of the overall group of RTx patients was not related to body composition and body fat distribution. Separate analyses for males and females showed a trend for a higher MMA (r=0.378, p=0.052) with an increasing SAI in males. In females, the SAI was inversely related to BMI (r=-0.408, p=0.048). Other body composition and body fat distribution parameters were not related to the SAI.
When using multiple regression analysis with FM, percentage of body fat, and BMI as dependent variables and age, time post-transplantation, daily and cumulative dose of prednisolone, LAI, OAI, and SAI as independent variables, the association between LAI and body fat, percentage body fat and BMI remained significant in female patients ($p<0.05$), whereas no significant relation was found between body composition and the other variables.

Nutrition and body composition

Parameters on nutrient intake of the RTx patients are shown in table 6.3. Male patients reported a significant higher energy intake than female patients. The energy percentages of carbohydrates and fat in the diet of males and females were not significantly different. The energy percentage of protein in the diet of females was significantly higher than in males.
Separate analyses for males showed an inverse relationship between total energy intake and percentage of body fat measured by DEXA and anthropometry (r=-0.425 and r=-0.426, respectively; p=0.022 and p=0.021, respectively) and a positive relation between total energy intake and LBM (r=0.428, p=0.021) and the percentage of LBM measured by DEXA and anthropometry, respectively (r=0.425 and r=0.426, respectively; p=0.022 and p=0.021, respectively). Furthermore, a positive relation was observed between the energy percentage of protein and the MMA (r=0.445, p=0.015). However,

after correction for physical activity, the significance of these correlations in the male RTx patients disappeared. No significant relations were found between body composition and body fat distribution and the energy percentages of carbohydrates and fat in the diet of the male RTx patients.
In females, no relations were observed between body composition and body fat distribution respectively and nutrient parameters.

Relation between body composition, blood pressure and lipid profiles

In the overall group, body FM, percentage of body fat (measured by DEXA), and BMI were significantly related to the mean arterial blood pressure ($r=0.436$, $r=0.339$ and $r=0.471$, respectively; $p<0.001$). No relation was found between the waist-to-hip ratio and mean arterial blood pressure. Serum high density lipoprotein cholesterol (HDL-cholesterol) was inversely related to the BMI ($r=-0.261$, $p=0.044$), whereas the serum triglyceride level was positively related to the waist-to-hip ratio ($r=0.282$, $p=0.025$).
Separate analyses for males showed a significant relationship between body FM and mean arterial blood pressure ($r=0.310$, $p=0.048$) and between BMI and mean arterial blood pressure ($r=0.377$, $p=0.014$). In females, body FM, percentage of body fat, and BMI were significantly related to the mean arterial blood pressure ($r=0.569$, $r=0.518$ and $r=0.547$, respectively; $p<0.01$). In contrast to males, the HDL-cholesterol in females was inversely related to the body FM, the percentage of body fat, the BMI, and the waist-to-hip ratio ($r=-0.488$, $r=-0.428$, $r=-0.464$, and $r=-0.438$, respectively; $p<0.05$) and the serum triglyceride level was positively related to body FM ($r=0.437$, $p=0.02$) and to BMI ($r=0.391$, $p=0.40$). The relations between the percentage of body fat measured by anthropometry and mean arterial blood pressure and lipid profile were the same as described above.

Discussion

In this cross-sectional study, we assessed the relation between steroids and body composition, REE and substrate oxidation rates, and the influence of physical activity and nutrient intake on body composition in stable RTx patients.

Steroid use and body composition

Body composition was measured by DEXA and by anthropometry. DEXA is a very useful technique for directly assessing soft tissue as well as bone. It has been shown to be of relatively high accuracy and very high precision[25-27].

However, DEXA is not assumption free: DEXA assumes that the hydration status of the LBM is uniform and fixed at 0.732 L/kg LBM[25,28]. Anthropometry (skinfold measurements) also assumes that the density of the LBM is normal, i.e., that the hydration status of the LBM is normal. In an earlier study, we found a good method agreement between DEXA and anthropometry for the measurement of body fat and fat-free mass in RTx patients[29].

In the present study, the percentage of total body fat in male and female RTx patients averaged 24.0% and 37.9%. Compared with the Dutch population, the percentage of body fat in the males is relatively normal, whereas the percentage of body fat in the female patients is fairly high[30,31].

It has been shown that in the general population the risk of metabolic abnormalities, hypertension, diabetes mellitus, cardiovascular disease, and death increases with an increase of body fat and especially when the waist-to-hip ratio rises above 1.00 for men and above 0.80 for women[32,33]. The mean waist-to-hip ratio was 0.92±0.07 in males and 0.82±0.07 in females. Of the males, 11.9% had a waist-to-hip ratio above 1.00. Of the females, 65.7% had a waist-to-hip ratio above 0.80. The prevalence of this risk indicator in our RTx population thus appears to be much higher in females than in males. In the present study, a significant, positive relationship was found between the waist-to-hip ratio and the serum triglyceride level of the RTx patients and an inverse relationship was found between the waist-to-hip ratio and the HDL-cholesterol level. Moreover, a significant, positive relationship was found between body FM, percentage of body fat and BMI on the one hand and mean arterial blood pressure on the other hand.

In the few studies that have addressed the impact of renal transplantation on body composition, weight gain, and especially an increase of body FM was observed[1-5,34]. However, whether these changes in body composition were due to the glucocorticosteroid immunosuppressive therapy after transplantation remained controversial.

It is generally known that long-term treatment with glucocorticoids may cause among others Cushingoid habitus, obesity, and muscle wasting[9]. In our study, in which patients on steroid-free immunosuppressive therapy were included, we did not find differences in FM, LBM and body fat distribution between RTx patients on 0-mg, 5-mg, and 10-mg maintenance steroid therapy, nor did we find significant relations between the cumulative steroid dosage and body composition and body fat distribution parameters in RTx patients, whereas we should state that inherent to the cross-sectional design of the study the different groups were not completely comparable in each aspect. The results might be biased by the fact that patients on 0-mg and 5-mg maintenance steroid dose were also using cyclosporine, whereas patients on 10 mg steroids did not. Moreover, mean age was higher in the patients on cyclosporine mono-therapy and time post-transplantation was higher in patients on 10 mg steroids,

whereas the LAI was significantly higher in patients on 10 mg steroids compared to patients on 0 mg steroids. However, when using multiple regression analysis with age, time post-transplantation, OAI, SAI, LAI, and cumulative and daily dose of prednisone as independent variables, the association between LAI and body fat remained significant in female patients, whereas no significant relation was found between body composition and the other variables. Our results are in agreement to the results of Qureshi et al.[35], which indicate that chronic use of low doses of corticosteroids in RTx patients seems to have no major clinical nutritional side-effects. Therefore, despite possible effects on muscle metabolism, long-term treatment with relatively low dosages of corticosteroids does not appear to have a large effect on FM and body fat distribution in RTx patients. Nevertheless, because DEXA and anthropometry give only relatively crude information on body composition, more subtle effects of low-dose corticosteroids on body composition cannot be excluded by the present study.

Steroid use, REE and substrate oxidation rates

We did not find differences in REE in RTx patients on 0-mg, 5-mg, and 10-mg maintenance steroid dosage. However, both in the overall group of RTx patients and in the 0-mg, 5-mg, and 10-mg maintenance dose groups, the energy expenditure expressed per kg LBM is slightly, but significantly, higher than the energy expenditure predicted by the Harris and Benedict equation[36]. Mathieu et al.[37] also found a higher REE (expressed per kg LBM) in RTx patients on cyclosporine mono-therapy (after discontinuation of prednisone) compared with healthy control subjects. Thus, the prednisolone immuno-suppressive therapy probably does not have a major effect on REE in the fasting state in RTx patients. Horber and collegues[38] also did not find an effect of prednisone treatment (0.8 mg/kg body weight for seven days) on REE in the fasting state in healthy, adult volunteers, whereas it should be stated that the daily steroid dose in their study is much higher compared with our study. Steiger et al.[2] found that fasting energy expenditure in RTx patients on prednisone immunosuppressive therapy also did not differ from healthy controls, both short after transplantation and during 15 months follow-up.

In addition, steroid treatment may affect body composition by inducing alterations in substrate oxidation. Horber et al.[38] found an increased protein oxidation and a decreased fat oxidation in healthy volunteers treated with prednisone. Steiger et al.[2] found a positive relation between protein oxidation and the daily steroid dose and an inverse relation between lipid oxidation and the daily steroid dose in RTx patients. In the our study, we did not find differences in protein oxidation between patients on 0-mg, 5-mg, and 10-mg maintenance steroid dose. Lipid oxidation in female patients, however, was

lower in patients on 5 mg steroids than in patients on steroid-free immunosuppressive therapy.
Long-term glucocorticoid therapy also causes disturbances in the glucose metabolism[10,39]. In the study of Horber et al.[38], prednisone treatment in healthy adults induced changes in plasma glucose, insulin, and c-peptide. Changes in glucose oxidation were, however, not observed. Steiger et al.[2] found a positive relationship between glucose oxidation and daily steroid dose in RTx patients. In our study, only in females glucose oxidation was higher in patients on 5-mg maintenance steroid therapy than in patients on steroid-free immunosuppressive therapy.
The maintenance dose of steroids used by our RTx patients, however, is relatively low compared to the steroid dosages used in the study of Horber et al.[38] (0.8 mg/kg body weight per day) and Steiger et al.[2] (0.1-0.5 mg/kg body weight per day), which might possibly be an explanation for the fact that we failed to find relations between steroid use and substrate oxidation in our group of RTx patients.

Physical activity and body composition

When studying the relationship between physical activity and body composition in our RTx population, we found a highly significant, positive relation between the percentage of LBM and leisure time physical activity especially in female transplant patients, in whom also a strong inverse relationship was found between leisure time physical activity and FM. In male RTx patients, a trend for a lower percentage of body fat and a higher percentage of LBM with an increasing level of occupational physical activity was observed. In female patients, sport activity level was inversely related to the BMI. In males, a trend for a higher upper arm muscle area with an increasing sport activity level was observed. Our results suggest that an increased level of physical activity may have favorable effects on the body composition of RTx patients.
These results are in agreement with studies to the relation between physical activity and body composition in the general population[13]. However, due to the cross-sectional design of the study, we cannot directly prove that a causal relationship exists between physical activity level and body composition in RTx patients.

Nutrient intake and body composition

The mean energy intake of both the male and female RTx patients appeared to be slightly lower than the mean energy intake of healthy, Dutch adults of the same age. The macronutrient composition of the ad libitum diet of the RTx patients and the diet of the healthy, age-matched, Dutch adults was comparable. The female RTx patients, however, reported to have a somewhat

higher carbohydrate intake and a lower fat intake[40]. The composition of the diet of the RTx patients satisfied to the Dutch Dietary Reference Intakes[41], in which a macronutrient composition of 30-35 energy percentages of fat, 50-55 energy percentages of carbohydrates, and 10-15 energy percentages of protein is recommended.
In our study, no relations were observed between nutrient intake and body composition and body fat distribution in RTx patients after correction for physical activity.

Conclusions

In this cross-sectional study, which included a group of RTx patients on steroid-free immunosuppressive therapy, we did not observe differences in body composition in patients treated with a maintenance dose of 0-mg, 5-mg, or 10-mg prednisolone per day, nor did we find a relation between the cumulative dosage and body composition measured by DEXA and anthropometry. Although REE was higher compared to the predicted values, no relation with steroid dosage was observed. Also substrate oxidation did not differ between patients on 0-mg, 5-mg, or 10-mg maintenance steroid doses, apart from small differences in glucose and lipid oxidation in the female RTx patients. In contrast, leisure time physical activity was highly, significantly related to the percentage of body fat and LBM, especially in female RTx patients.
Thus, especially an increase of physical activity might have a beneficial effect on body composition in RTx patients. This effect appears to be more pronounced in female patients than in male patients. Future prospective studies should address the impact of training programs on physical performance and body composition in RTx patients.

References

1. Verran D, Munn S, Collins J, Hill G. Impact of renal allograft implantation and immunosuppression on body composition using in vivo neutron activation analysis. Transplant Proc 1992; 24(1):173-174.
2. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger Ph, Horber FF. Body composition and fuel metabolism after kidney transplantation. Eur J Clin Invest 1995; 25:809-816.
3. Hart PD, Wilkie ME, Edwards A, Cunningham J. Dual energy X-ray absorptiometry versus skinfold measurements in the assessment of total body fat in renal transplant recipients. Eur J Clin Nutr 1993; 47:347-352.
4. Isiklar I, Akin O, Niron EA. Effects of renal transplantation on body composition. Transplant Proc 1998; 30:831-832.
5. Martin M, Lopes IM, Errasti P, Martinez JA. Body composition and biochemical profile as affected by diet and renal transplantation among renal patients. J Physiol Biochem 1998; 54(1):53-54.
6. Gunnarson R, Lofmark R, Nordlander R, Nyquist O, Groth CG. Acute myocard infarction in renal transplant recipients: incidence and prognosis. Eur Heart J 1984; 5:218-221.
7. Raine AEG, Margreiter R, Brunner FP, Ehrich JH, Geerlings W, Landais P, Loirat C, Mallick NP, Selwood NH, Tufveson G. Report of managment of renal failure in Europe, XXII 1991. Nephrol Dial Transplant 1992; 7(Suppl 2):7-35.
8. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7:158-165.
9. Danovitz GM. Immunosuppressive medications and protocols for kidney transplantation, in Handbook of kidney transplantation. Danovitz GM, Editor. Little Brown and Compagny, Boston. 1992:67-104.
10. Yanovski JA, Gordon BC. Glucocorticoid action and the clinical features of Cushing's syndrome. Endocrinol Metab Clin North Am 1994; 23(3):487-509.
11. Peeke PM, Chrousos GP. Hypercortisolism and obesity. Ann N Y Acad Sci 1995; 771: 665-676.
12. Prentice AM, Jebb SA. Obesity in Britain: gluttony or sloth? BMJ 1995; 311:437-439.
13. Wilmore JH. Increasing physical activity: alterations in body mass and composition. Am J Clin Nutr 1996; 63(Suppl 3):S456-460.
14. Epstein LH, Wing RR. Aerobic exercise and weight. Addict Behav 1980; 5:371-378.
15. Wilmore JH. Body composition in sport and exercise: directions for future research. Med Sci Sports Exerc 1983; 15:21-31.
16. Ballor DL, Keesey RE. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat free mass in males and females. Int J Obes 1991; 15:717-726.
17. Kohrt WM, Malley MT, Dalsky GP, Holloszy JO. Body composition of healthy sedentary and trained, young and older men and women. Med Sci Sports Exerc 1992; 24(7):832-837.
18. Painter P, Messer-Rehak D, Hanson P, Zimmerman SW, Glass NR. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron 1986; 42:47-51.
19. Kettner-Melsheimer A, Weiß M, Huber W. Physical work capacity in chronic renal disease. Int J Artif Organs 1987; 10(1):23-30.
20. Durnin JVGA, Womersly J. Body fat assessed from total body density and its estimation from skinfold thickness measurements in 481 men and women aged from 16 to 72 years. Br J Nutr 1974; 32:77-97.
21. Siri WE. The gross composition of the body, in Advances in biological and medical physics. Tobias CA, Lawrence JH, Editors. Academic Press, New York. 1956:239-280.
22. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949; 109:1-9.
23. Jequier E. Measurement of energy expenditure in clinical nutrition assessment. J Parent Enteral Nutr 1987; 11(Suppl 5):S86-89.
24. Baecke JAH, Burema J, Frijters JER. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982; 36:936-942.

25. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy X-ray absorptiometry for total body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990; 51:1106-1112.
26. Svendsen OL, Haarbo J, Hassanger C, Christiansen C. Accuracy of measurements of body composition by dual-energy X-ray absorptiometry in vivo. Am J Clin Nutr 1993; 57:605-608.
27. Jensen MD, Kanaley JA, Roust LR, O'Brien PC, Braun JS, Dunn WL, Wahner HW. Assessment of body composition with use of dual-energy X-ray absorptiometry: evaluation and comparison with other methods. Mayo Clin Proc 1993; 68:867-873.
28. Lohman TG. Dual energy X-ray absorptiometry, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:63-78.
29. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry. J Am Soc Nephrol 1999, 10:1067-1079.
30. Seidell JC, Groot LPGM de, Sonsbeek JLA van, Deurenberg P, Hautvast JG. Associations of moderate and severe overweight with self-reported illness and medical care in Dutch adults. Am J Publ Health 1986; 76:264-269.
31. Oosterlee A, Doornbos G, Seidell JC. Vetverdeling in samenhang met risico-indicatoren voor hart- en vaatziekten. T Soc Gezondheidsz 1987; 65:90-95.
32. Björntop P. Obesity and the risk of cardiovascular disease. Ann Clin Res 1985; 17:3-9.
33. Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntop P, Tibblin G. Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: a 13 year follow-up of participants in the study of men born in 1913. BMJ 1984; 288:1401-1404.
34. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, Rocher LL, Campbell DA. Obesity and renal transplantation. Surg Gynecol Obstet 1991; 172:367-376.
35. Qureshi AR, Lindholm B, Alvestrand A, Bergstrom J, Tollemar J, Hultman E, Groth CG. Nutritional status, muscle composition and plasma and muscle free amino acids in renal transplant patients. Clin Nephrol 1994; 42(4):237-245.
36. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Carnegie Institute of Washington, Washington. 1919.
37. Mathieu RL, Casez JP, Jaeger P, Montandon A, Peheim E, Horber FF. Altered body composition and fuel metabolism in stable kidney transplant patients on immunosuppressive monotherapy with cyclosporine A. Eur J Clin Invest 1994; 24(3):195-200.
38. Horber FF, Marsh HM, Haymond MW. Differential effects on prednisone and growth hormone on fuel metabolism and insulin antagonism in humans. Diabetes 1991; 40:141-149.
39. Olefsky JM, Kimmerling A. Effects of glucocorticoids on carbohydrate metabolism. Am J Med Sci 1976; 271:202-210.
40. Zo eet Nederland. Resultaten van de voedselconsumptie-peiling 1997-1998. Voorlichtingsbureau voor de Voeding. Den Haag. 1998.
41. Food and Nutrition Council of The Netherlands Dietary Reference Intakes 1989. The Hague.

Chapter 7

Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients

ECH van den Ham, JP Kooman, AMWJ Schols, FHM Nieman, JD Does, FME Franssen, MA Akkermans, PP Janssen, JP van Hooff

American Journal of Transplantation 2005; 5:1957-1965

Abstract

Background
Exercise intolerance is common in hemodialysis and renal transplant patients. Aim of the study was to assess to what extent exercise capacity and skeletal muscle strength of renal transplant patients differ from hemodialysis patients and healthy controls and to elucidate potential determinants of exercise capacity in renal transplant patients.

Patients and methods
Exercise capacity, muscle strength, lean body mass, and physical activity level were measured by cycle-ergometry, isokinetic dynamometry, dual energy x-ray absorptiometry, and Baecke questionnaire, respectively, in 35 renal transplant patients, 16 hemodialysis patients and 21 healthy controls.

Results
VO_2peak and muscle strength of the renal transplant patients were significantly lower compared to controls ($p<0.01$), but not different compared to hemodialysis patients. In renal transplant patients, strength ($p<0.001$), physical activity level ($p=0.001$), and age ($p=0.045$) were significant predictors of VO_2peak. Muscle strength was related to lean body mass ($p=0.001$) and age ($p=0.001$), whereas gender ($p<0.001$) and renal function ($p=0.01$) turned out to be significant predictors of lean body mass. No effects of corticosteroids were observed.

Conclusions
Exercise capacity and muscle strength seem equally reduced in renal transplant and hemodialysis patients compared to controls. In renal transplant patients, muscle strength and physical activity level are highly related to exercise capacity. Renal function appears to be a significant predictor of lean body mass, and through the lean body mass, of muscle strength and exercise capacity.

Introduction

Exercise intolerance is common in patients with end-stage renal disease receiving chronic hemodialysis (HD) and severely compromises quality of life. Although exercise capacity improves after renal transplantation, it often remains subnormal[1,2].

Potential factors influencing exercise capacity in HD patients are factors related to the uremic state or to the dialysis treatment itself, such as anemia, malnutrition, inflammation, and oxidative stress. Also skeletal muscle wasting is described. Muscle protein breakdown is commonly found in HD patients[3-5]; there is persuasive evidence that factors such as metabolic acidosis, resistance to anabolic hormones, and the presence of a chronic inflammatory state cause muscle protein degradation by activating the ubiquitin-proteosome pathway[5,6]. Successful renal transplantation corrects or improves many of the systemic manifestations mentioned above; however, the use of corticosteroids as immunosuppressive therapy and the often subnormal renal function can still lead to abnormalities in body composition of renal transplant (RTx) patients, in particular to a decreased muscle mass. In general, an increase in body weight is observed after renal transplantation[7-9], but at least in the first months after renal transplantation this increase appears to be predominantly due to an increase in fat mass (FM)[10-12]. Moreover, physical inactivity can enhance detrimental effects on skeletal muscle function in RTx and HD patients[13-15].

In an earlier study, we observed a relatively low level of physical activity in RTx patients[16]. The relative contribution of muscle mass, muscle strength, physical activity level (PAL), the use of corticosteroids and a subnormal renal function to exercise capacity in RTx patients has however not been studied yet. We hypothesized that the severity of muscular weakness and exercise intolerance is less in RTx patients compared to HD patients, but worse compared to healthy controls. Moreover, we hypothesized that physical inactivity and possibly the use of corticosteroids and a subnormal renal function are important determinants of exercise intolerance in RTx patients.

The aim of the present study was 1) to assess to what extent exercise capacity and skeletal muscle strength of RTx patients differ from HD patients and age-matched, untrained, healthy subjects and 2) to elucidate potential determinants of exercise capacity in RTx patients.

Patients and methods

Patients

Thirty-five RTx patients, 16 HD patients and 21 age-matched, untrained, healthy subjects (controls) were included in this study. Age ranged from 21 to 71 years. All renal patients were in clinically stable condition. In RTx patients, transplantation occurred at least six months before start of the study. HD patients had been treated with hemodialysis for at least three months, were receiving regular renal replacement therapy three times weekly (Kt/V at least 1.2), and were on the waiting list for renal transplantation. Exclusion criteria for the study were hemoglobin <6.3 mmol/l, diabetes mellitus, malignancies or history of malignancy (except nonmetastatic basal or squamous cell carcinoma of the skin that had been treated successfully), known history of heart disease (congestive heart disease, evidence of coronary artery disease, signs or symptoms of peripheral vascular disease), organ transplant other than kidney, use of corticosteroids for any reason other than kidney transplantation, musculoskeletal problems, and other contra-indications for exercise testing.
Eligible RTx and HD patients were asked to participate in the study at the outpatients' clinic and at six hemodialysis departments in our region, respectively. Controls were partners of patients (n=11) and volunteers recruited by advertisement; they were examined by a physician to rule out significant pulmonary, cardiac or other complaints.
Written informed consent was obtained from each patient and control subject prior to participation. The study was approved by the Ethical Committee of the Maastricht University Hospital.

Methods

Exercise capacity

The renal patients and controls performed a symptom-limited graded cycle-ergometry test to define their maximal exercise capacity (in HD patients on the first nondialysis day after the day patients had been treated with hemodialysis). After a period of rest and one minute of unresisted cycling, a progressively increasing work rate test was started in order to determine peak work rate (Wpeak) and peak oxygen uptake (VO_2peak), both important indicators of exercise capacity. The work rate increase ranged from 10 to 25 W/min in renal patients and from 10 to 30 W/min in controls, so that the length of the test was comparable for all subjects. Exercise load was not known by the subjects. All subjects were encouraged to pedal with a frequency of 60-70 rpm until exhaustion. During exercise testing, expired gases were analyzed using breath-by-breath analysis with a breathing mask (Oxycon Beta®, Jaeger,

Würzburg, Germany). Furthermore, the ECG, systolic and diastolic blood pressure, heart rate (HR) and percutaneous oxygen saturation were monitored. The test was terminated when the subjects complained of limiting fatigue, dyspnea or if changes in ECG occurred, systolic blood pressure (BPr) exceeded 250 mmHg, diastolic BPr was 120 mmHg or higher, or BPr decreased 20 mmHg or more.

VO_2peak (expressed as ml O_2/min) was defined as the highest recorded oxygen uptake at peak exercise. VO_2peak was also expressed relative to body weight and muscle mass (i.e., ml O_2/min/kg). Peak heart rate reserve (HRRpeak) was calculated as predicted maximum HR minus observed maximum HR[17].

Skeletal muscle strength

Muscle strength of the dominant knee extensor (quadriceps femoris) was measured using a Cybex II plus (Lumex, Inc., Ronkonkoma, NY) isokinetic dynamometer. Subjects were seated upright in the chair of the dynamometer and had to keep their hands on their thighs during testing. Before testing, each subject was familiarized in a standardized way with the equipment and the test procedure. Maximal muscle strength was defined as the highest peak torque (Nm) of 15 consecutive maximal contractions at an angle velocity of 90º/sec. Muscle strength was expressed in absolute terms as well as relative to muscle mass of the legs.

Body composition

Dual energy x-ray absorptiometry (DEXA; DPX-L, Lunar Radiation Corp., Madison, WI) was used for the measurement of whole-body composition, i.e., FM, lean body mass (LBM, comprising muscle, inner organs, and body water) and bone mineral content (BMC)[18]. In HD patients, DEXA measurements were performed on the first nondialysis day after the day patients had been treated with hemodialysis. Body weight was computed as the sum of FM, LBM, and BMC. LBM was used as an estimate of muscle mass. Body mass index (BMI) was calculated as body weight (kg) divided by squared body height (m^2).

Multi-frequency bio-electrical impedance analysis

Multi-frequency bio-electrical impedance analysis (Xitron 4000B, Xitron Technologies Inc., San Diego, CA) was used to determine the volume of the intracellular (ICW), extra-cellular (ECW), and total body water (TBW) compartment. Impedance measurements were performed in supine position, in a standard fashion (as earlier described[18]) and for HD patients on the first nondialysis day after the day patients had been treated with hemodialysis.

Hematological and biochemical blood parameters

Blood samples were taken both in renal patients and controls (in HD patients just before start of dialysis treatment). The routine parameters hemoglobin, creatinine, urea, albumin, and glucose and the inflammatory marker C-reactive protein (CRP) were assessed in all participants. In renal patients, sodium, potassium, calcium, phosphate and parathyroid hormone (PTH) were assessed too. CRP was determined by high-sensitivity particle-enhanced immuno-nephelometry[19]. Other blood tests were performed according to standard laboratory procedures.

Renal function

The formula of Cockcroft and Gault[20] was used to estimate creatinine clearance in the RTx and control group. In RTx patients, renal function was also determined by calculating the creatinine clearance from 24-hr urine volume and creatinine levels in plasma and 24-hr urine.

Physical activity level

The habitual PAL was assessed by means of the Baecke questionnaire[21]. This short questionnaire consists of 16 items concerning occupation (eight items), sport (four items), and leisure time activities excluding sport (four items). Scores on the occupational, sport, and leisure time items are used to calculate the occupational activity index (OAI), sport activity index (SAI), and leisure activity index (LAI), respectively. Each index ranges from 1 to 5, with a higher index score indicating a higher level of activity. Individuals not reporting any occupational activity were assigned an OAI of 1. Total activity index (TAI) was calculated as the sum of OAI, SAI, and LAI.

Statistics

Comparison of the groups: RTx versus HD and controls

Kolmogorov-Smirnov tests were used to test for normal distribution. Nonparametric Kruskal-Wallis tests (if necessary, followed by Mann-Whitney *U* tests) were used to compare not normally distributed variables of the RTx, HD and control group. Approximately normally distributed variables were compared by one-way analysis of variance (ANOVA) with correction for pairwise multiple comparisons via post hoc Bonferroni tests (in case of equal variances of the dependent variable across the groups) or Dunnett T3 tests (in case of unequal variances). Two-way ANOVA followed by Bonferroni's or Dunnett T3's pairwise multiple comparisons procedure was used to determine gender-corrected differences in exercise capacity, muscle function, and body composition between the groups. Differences for discrete variables between groups were assessed with the log-likelihood Chi-Square test. Pearson product-moment

correlations were used to assess relationships between metric and/or dichotomous variables.

Relationships of exercise capacity with potential predictors in RTx patients

Stepwise regression analysis was used to determine significant predictors of exercise capacity. To facilitate data analysis on the relationship between parameters of exercise capacity at one hand and parameters from skeletal muscle strength and body composition, renal function, use of corticosteroids, and habitual PAL on the other hand, a nonrecursive hypothetical model was used. The assumption of nonrecursiveness, i.e., of asymmetrical relationships within this model, constrains the number of possible relationships between the many multidisciplinary observed parameters. Data analysis can further be simplified by assuming linear relationships between all metrically measured parameters. Dummy regression analysis in which the use of corticosteroids was entered as a dummy variable (no steroids=0; steroids=1) was used to estimate the relationships between the parameters. Standardized regression coefficients (beta's) are used to characterize the strength of the resulting relationships within the final model.

Data are expressed as mean±SD, unless indicated otherwise. Statistical analysis was performed by SPSS for Windows, version 11.5. P-values <0.05 were considered to be statistically significant.

Results

Patient characteristics

Characteristics of patients and controls are shown in table 7.1. Groups were not significantly different for age and gender. Body weight and BMI of the RTx patients were not significantly different from body weight and BMI of HD patients and controls. RTx patients had a significantly lower renal function than controls ($p<0.01$). Blood parameters related to renal function (i.e., creatinine, urea, electrolytes, PTH) were, as expected, significantly different between the RTx and HD patients; creatinine and urea were also significantly different in RTx patients and controls. Hemoglobin levels in RTx patients were significantly higher than in HD patients ($p<0.01$), but similar to controls. Glucose, albumin, and CRP levels were not significantly different between the groups.

Table 7.1 Patient demographics

	RTx (n=35)	HD (n=16)	Controls (n=21)
Age (yr)	52.3 ± 10.4	49.0 ± 11.9	54.9 ± 10.8
Gender (M/F)	18 / 17	10 / 6	11 / 10
Body weight (kg)	74.2 ± 15.6	67.6 ± 13.2[j]	80.7 ± 13.1
BMI (kg/m^2)	25.7 ± 4.1	23.3 ± 3.3[i]	26.9 ± 3.4
Time after Tx (months)	84.3 ± 80.4[f]	-	-
Time on dialysis prior to Tx (months)	24.1 ± 20.1[g]	-	-
Time on dialysis (months)	-	24.8 ± 18.3[k]	-
Creatinine clearance (ml/min)[a]	58.6 ± 17.2[h]	-	105.1 ± 25.5
Creatinine clearance (ml/min)[b]	60.8 ± 20.2	-	-
Smoking	5 (14.3%)	6 (37.5%)	6 (28.6%)
Blood parameters			
Hemoglobin (mmol/l)	8.6 ± 1.0	7.5 ± 0.7[il]	8.9 ± 0.8
Creatinine (µmol/l)[c]	138 ± 54[h]	993 ± 359[hm]	76 ± 12
Urea (mmol/l)	8.8 ± 4.0[i]	23.1 ± 6.7[il]	4.6 ± 0.9
Albumin (g/l)	41.7 ± 3.2	40.1 ± 4.5	42.1 ± 2.4
Glucose (mmol/l)[c]	5.7 ± 0.9	5.7 ± 1.2	5.5 ± 0.7
CRP (mg/l)	3.8 ± 3.3	6.8 ± 10.0	3.5 ± 3.3
Sodium (mmol/l)	139.4 ± 1.8	137.8 ± 3.0	-
Potassium (µmol/l)	4.5 ± 0.5	4.9 ± 0.6[m]	-
Calcium (mmol/l)	2.43 ± 0.16	2.33 ± 0.18[n]	-
Phosphate (mmol/l)	1.09 ± 0.32	1.80 ± 0.56[m]	-
PTH (mmol/l)	9.6 ± 4.5	15.9 ± 9.5[n]	-
Causes of renal failure			
Chronic glomerulonephritis	16 (45.7%)	7 (43.8%)	-
Pyelonephritis / interstitial nephritis	3 (8.6%)	1 (6.3%)	-
Nephrosclerosis	4 (11.4%)	2 (12.5%)	-
Polycystic kidney disease	7 (20.0%)	4 (25.0%)	-
Congenital sphincter sclerosis	1 (2.9%)	-	-
Unknown	4 (11.4%)	2 (12.5%)	-
Medication use			
Steroid-based immunosuppression[d]	17 (48.6%)	-	-
Steroid-free immunosuppression[e]	18 (51.4%)	-	-
β-blockers	24 (68.6%)	7 (43.8%)	-
Erythropoetin	-	14 (88.0%)	-

Data given as mean ± SD or as number of patients (% of patients); [a] calculated by Cockcroft and Gault formula; [b] calculated from 24-hr urine volume and creatininelevels in plasma and 24-hr urine; [c] data not normally distributed; [d] prednisolone (5-10 mg/day) in combination with FK-506 or Cyclosporin-A; [e] FK-506 or Cyclosporin-A mono-therapy; [f] median time after Tx=46.9 months (range 8.7-289.3 months); [g] median time on dialysis prior to Tx (n=33; two patients preemptive RTx)=19.1 months (range 0.7-84.0 months); [h] p<0.01 versus controls; [i] p<0.01 versus controls, corrected for gender; [j] p<0.05 versus controls, corrected for gender; [k] median time on dialysis=18.7 months (range 3.0–66.0 months); [l] p<0.01 versus RTx, corrected for gender; [m] p<0.01 versus RTx; [n] p<0.05 versus RTx; BMI=body mass index; Tx=transplantation; CRP=C-reactive protein; PTH=parathyroid hormone.

Comparison of the groups: RTx versus HD and controls

Exercise capacity

None of the cycle-tests had to be terminated because of changes in ECG, hypertension, or other adverse events. Maximal achieved workload (Wpeak) of RTx and HD patients was not significantly different; RTx patients scored, however, lower than controls ($p<0.01$) (table 7.2). VO_2peak (in absolute terms as well as adjusted for LBM) of the RTx patients was also significantly lower compared to that of controls ($p<0.01$), but no significant difference was observed between RTx and HD patients. The respiratory coefficient at Wpeak was not significantly different in the groups. Only controls reached their predicted maximal peak heart rates (HRpeak). Exercise capacity (both Wpeak and VO_2peak) of the renal patients using β-blockers was not significantly different from that of the renal patients not using β-blockers.

Skeletal muscle strength

Quadriceps strength of the RTx and HD patients (in absolute terms as well as adjusted for LBM) was not significantly different (table 7.2). The absolute muscle strength of the RTx patients was, however, significantly lower than that of controls ($p<0.01$). A trend for a lower adjusted muscle strength was observed in RTx patients compared to controls ($p=0.07$).

Table 7.2 Exercise capacity and skeletal muscle strength in RTx patients, HD patients and controls

	RTx (n=35)	HD (n=16)	Controls (n=21)
Exercise capacity:			
Wpeak (Watt)	132 ± 51[a]	113 ± 52[a]	176 ± 62
VO_2peak (ml/min)	1570 ± 566[a]	1492 ± 720[a]	2153 ± 793
VCO_2peak (ml/min)	1807 ± 679[a]	1755 ± 883[a]	2481 ± 984
VO_2peak (ml/min/kg BW)	21.3 ± 6.2[b]	21.4 ± 8.0[c]	26.4 ± 7.8
VO_2peak (ml/min/kg LBM)	33.1 ± 8.0[b]	30.5 ± 9.8[a]	41.0 ± 10.6
RER-peak	1.15 ± 0.08	1.17 ± 0.10	1.14 ± 0.09
HRpeak (bpm)	138 ± 26[a]	136 ± 27[a]	167 ± 19
HRRpeak (bpm)	31 ± 24[a]	35 ± 24[a]	-2 ± 16
Skeletal muscle strength:			
Quadriceps strength (nM)	88.7 ± 30.4[a]	78.8 ± 35.6[a]	116.3 ± 37.5
Quadriceps strength (nM/kg LM legs)	5.7 ± 1.3 [c]	5.2 ± 1.7[b]	6.7 ± 1.4

Data given as mean ± SD; [a] $p<0.01$ versus controls, corrected for gender; [b] $p<0.05$ versus controls, corrected for gender; [c] $p=0.07$ versus controls, corrected for gender; W=workload; BW=body weight; LBM=lean body mass; VO_2=oxygen uptake; VCO_2=carbon dioxide production; RER=respiratory exchange ratio; HR=heart rate; bpm=beats per minute; HRR=heart rate reserve; LM=lean mass.

Body composition

Body weight and LBM of the RTx patients were not significantly different compared to HD patients and controls (table 7.3). FM of the RTx patients was considerably higher, although not statistically significant, compared to HD patients (p=0.07), but not significantly different compared to controls. FM relative to body weight was not significantly different between the groups, just like the ECW, ICW, and the ratio ECW/TBW.

Table 7.3 Body composition of the RTx patients, HD patients and controls

	RTx (n=35)	HD (n=16)	Controls (n=21)
Body weight (kg)	74.2 ± 15.6	67.6 ± 13.2[a]	80.7 ± 13.1
LBM (kg)	47.9 ± 9.8	47.1 ± 11.4	51.3 ± 11.4
FM (kg)	24.2 ± 10.6	17.9 ± 5.6[a]	25.4 ± 8.1
BF (% of BW)	31.8 ± 9.1	26.8 ± 8.1	32.1 ± 9.1
BMC (kg)	2.6 ± 0.6[a]	2.5 ± 0.6[a]	3.0 ± 0.6
ECW (l)	20.4 ± 3.6	18.9 ± 3.4	21.3 ± 4.2
ICW (l)	15.7 ± 4.0	15.7 ± 5.1	17.7 ± 4.3
ECW/TBW	0.57 ± 0.04	0.55 ± 0.05	0.55 ± 0.02

Data given as mean ± SD; [a] p<0.05 versus controls, corrected for gender; LBM=lean body mass; FM=fat mass; BF=body fat; BW=body weight; BMC=bone mineral content; ECW=extra-cellular water; ICW=intracellular water; TBW=total body water.

Physical activity level

The total activity index (TAI) in the RTx group was not significantly different from the TAI in the HD and control group (table 7.4).

Table 7.4 Habitual physical activity level of the RTx patients, HD patients and controls

	RTx (n=35)	HD (n=16)	Controls (n=21)
Occupational activity index (OAI)	2.3 ± 0.9	1.9 ± 1.0	2.6 ± 0.7
Sport activity index (SAI)	2.2 ± 0.8	1.8 ± 0.6[a]	2.5 ± 0.8
Leisure time activity index (LAI)	2.6 ± 0.6	2.5 ± 0.7	2.7 ± 0.5
Total activity index (TAI)	7.2 ± 1.5	6.2 ± 1.5[b]	7.8 ± 1.4

Data given as mean ± SD; [a] p<0.05 versus controls, corrected for gender; [b] p<0.01 versus controls, corrected for gender.

Comparison of RTx patients with and without steroids

Seventeen RTx patients were using steroid-based immunosuppression (ST+, maintenance dosage 5-10 mg/day) and 18 RTx patients were using steroid-free immunosuppression (ST-) at the moment of testing. Exercise capacity, skeletal muscle strength, body composition, and PAL of the ST+ and ST- group were not significantly different (table 7.5). Groups were comparable for age, gender, and renal function.

Table 7.5 Exercise capacity, muscle strength, body composition and physical activity level in RTx patients using steroid-based immunosuppression and RTx patients on steroid-free immunosuppression

	ST+ (n=17)	ST- (n=18)
Exercise capacity		
Wpeak (Watt)	132 ± 52	131 ± 51
VO_2peak (ml/min)	1543 ± 620	1597 ± 523
VCO_2peak (ml/min)	1790 ± 722	1823 ± 654
VO_2peak (ml/min/kg BW)	21.2 ± 6.2	21.5 ± 6.4
VO_2peak (ml/min/kg LBM)	32.8 ± 7.3	33.5 ± 8.8
RER-peak	1.17 ± 0.07	1.13 ± 0.08
HRpeak (bpm)	138 ± 25	139 ± 28
HRRpeak (bpm)	30 ± 23	30 ± 26
Skeletal muscle strength		
Quadriceps strength (nM)	84.6 ± 27.2	92.2 ± 33.2
Quadriceps strength (nM/kg LM legs)	5.4 ± 0.9	6.0 ± 1.6
Body composition		
Body weight (kg)	73.1 ± 17.4	75.3 ± 14.1
LBM (kg)	47.7 ± 9.5	48.1 ± 10.2
FM (kg)	23.6 ± 12.3	24.7 ± 9.0
BF (% of BW)	31.1 ± 10.4	32.5 ± 8.1
BMC (kg)	2.6 ± 0.6	2.5 ± 0.6
ECW (l)	20.6 ± 3.6	20.2 ± 3.7
ICW (l)	15.6 ± 3.4	15.8 ± 4.6
ECW/TBW	0.57 ± 0.04	0.57 ± 0.05
Physical activity level		
OAI	2.3 ± 0.8	2.4 ± 0.9
SAI	2.1 ± 0.8	2.4 ± 0.8
LAI	2.6 ± 0.7	2.5 ± 0.6
TAI	7.1 ± 1.2	7.3 ± 1.7

Data given as mean ± SD; ST+=steroid-based immunosuppression; ST-=steroid-free immunosuppression; W=work rate; VO_2=oxygen uptake; VCO_2=carbon dioxide production; BW=body weight; LBM=lean body mass; RER=respiratory exchange ratio; HR=heart rate; bpm=beats per minute; HRR=heart rate reserve; LM=lean mass; FM=fat mass; BF=body fat; BMC=bone mineral content; ECW=extra-cellular water; ICW=intracellular water; TBW=total body water; OAI=occupational activity index; SAI=sport activity index; LAI=leisure time activity index; TAI=total activity index.

Six patients in the ST- group had been off steroids for less than one year at the moment of testing; the cumulative dosage of steroids which they did receive, was, however, relatively low (on the average 1.5±0.4 g). The other 12 patients in the ST- group had been off steroids for more than one year (on the average 31.8±18.2 months). Comparison of the RTx patients in the ST+ group and the RTx patients who were off steroids for more than one year, showed no significant differences in exercise capacity, muscle strength, body composition, and PAL either (results not shown).

Relationships of exercise capacity with potential predictors in RTx patients

Parameters of exercise capacity are summarized in a regression analysis model including clinical and habitual physical activity parameters (figure 7.1). Final results of the regression analysis on VO_2peak (ml/min), muscle strength of the quadriceps femoris (Nm) and LBM (kg) in RTx patients are given in table 7.6.

Muscle strength was strongly and significantly related to VO_2peak (r=0.866, p<0.001). In addition to muscle strength (p<0.001), PAL and age appeared to be significant predictors of VO_2peak in regression analysis (p=0.001 and 0.045, respectively). There was no direct regression effect of LBM on VO_2peak: the strong correlation between VO_2peak and LBM (r=0.673, p<0.001) was explained by the strong, positive regression effect of LBM with muscle strength (p=0.001).

Renal function (calculated from 24-hr urine volume and creatinine levels in plasma and 24-hr urine) turned out to be a significant predictor of LBM (p=0.01) and via LBM, of muscle strength and exercise capacity. The lower the creatinine clearance, the lower the LBM and consecutively the skeletal muscle strength and exercise capacity. No significant relationship was observed between the use of corticosteroids and LBM, muscle strength or exercise capacity. Hemoglobin and CRP levels, and the 'time after renal transplantation' did not affect any of these parameters either.

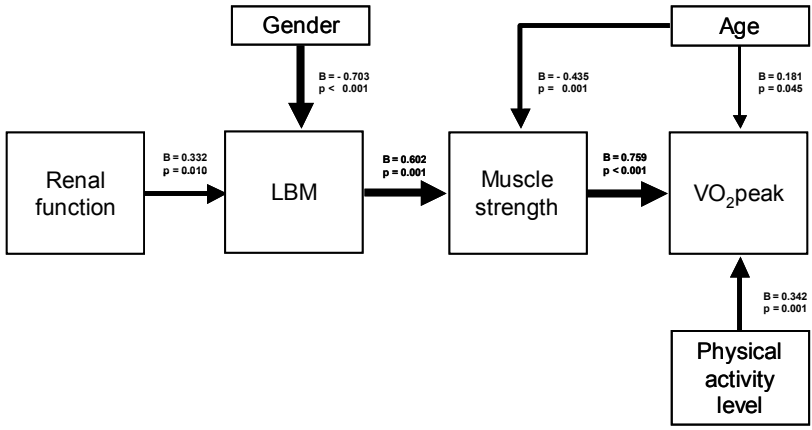


Figure 7.1 Final regression analysis results using VO_2peak as an indicator for exercise capacity in RTx patients. Arrows indicate significant relationships: the bolder the arrow, the stronger the relative contribution of the predictor. Furthermore, the corresponding standardized beta coefficients and their significance levels are given. Muscle strength indicated by quadriceps strength, physical activity level by total activity index (TAI). Gender coded as males=0 and females=1. LBM=lean body mass.

Table 7.6 Regression model results for VO_2peak, muscle strength, and LBM in RTx patients[a]

	Regression coefficient	SE	Beta	P
Model 1: VO_2peak (ml/min)[b]				
Age (yr)	11.13	5.27	0.181	0.045
Gender[c]	-50.83	103.27	-0.044	0.627
Muscle strength (Nm)	14.20	1.98	0.759	<0.001
Physical activity level[d]	129.87	33.78	0.342	0.001
Intercept	-1169.48	447.89	-	0.015
Model 2: Muscle strength (Nm)[b]				
Age (yr)	-1.32	0.38	-0.435	0.001
Gender[c]	-2.26	9.96	-0.037	0.822
LBM (kg)	1.88	0.51	0.602	0.001
Intercept	70.40	34.33	-	0.050
Model 3: LBM (kg)[b]				
Age (yr)	0.06	0.11	0.062	0.611
Gender [c]	-13.55	2.33	-0.703	<0.001
Renal function[e] (ml/min)	0.169	0.06	0.332	0.010
Intercept	40.79	7.42	-	<0.001

[a] age and gender were always kept into the regression models, regardless of the fact they had significant or nonsignificant effects; [b] R^2 model 1=0.856, p=0.001; R^2 model 2=0.576, p=0.001; R^2 model 3=0.567, p=0.010; [c] gender: males=0, females=1; [d] physical activity level=score on total activity index (TAI) Baecke questionnaire; [e] renal function=creatinine clearance calculated from 24-hr urine volume and creatinine levels in plasma and 24-hr creatinine; LBM=lean body mass.

Discussion

In the present study, we assessed differences in exercise capacity and skeletal muscle strength between RTx and HD patients and between RTx patients and healthy, age-matched controls. Furthermore, we investigated the relationship between exercise capacity and its potential predictors.

Exercise capacity of RTx patients was found to be comparable to the exercise capacity of HD patients, but significantly lower (approximately 30%) compared to controls. In the HD patients, VO_2peak expressed per kilogram body weight was 21.4±8.0 ml/min/kg; this is in line with previous reported VO_2peak levels in HD patients, which were in the range of approximately 15 to 22 ml/min/kg[22-26]. As also described by Sietsema et al.[25], the wide range of the VO_2peak values for HD patients previously reported might be due to differences in test-modalities for VO_2peak and characteristics of the study populations. In the present study, only stable patients on the waiting list for renal transplantation, without severe co-morbidity, were included; therefore, VO_2peak values are relatively high. Considerably less is known about the VO_2peak levels of RTx patients. Earlier studies reported VO_2peak levels ranging from approximately

24 to 32 ml/min/kg[1,27-30]. The VO_2peak levels of the RTx patients in the present study (21.3±6.2 ml/min/kg) seem to be somewhat lower compared to levels reported in the literature; the age of the patients included in those studies was on the average, however, circa 10 years lower. A possible reason for nonsignificance between the RTx and HD group may be the unsatisfactory power of our test.

Both renal patients and controls did make a maximal effort during the exercise test, since the mean respiratory exchange ratio at peak exercise was above 1.1 in all groups, indicating high-intensity, lactate-acidosis-induced exercise. In renal patients, HRpeak is not appropriate to verify patients' efforts during exercise testing, because many of them are using β-blockers for treatment of hypertension and, specifically in HD patients, because of their limited chronotropic exercise response, possibly as a consequence of autonomic neuropathy[27,31].

In fact it is possible that the exercise capacity of the HD patients did deteriorate and that the exercise capacity of the RTx patients did improve since the time of starting hemodialysis c.q. since the time of transplantation. Given the cross-sectional design of the study, and inherent in this design the lacking of pre-dialysis and pre-transplant data, it is not possible to study changes in exercise capacity over time. For this, a longitudinal study has to be performed.

In chronic heart failure, patients with VO_2peak values <20 ml/min/kg body weight are classified as having functional limitations[32]. In the present study, 49% of the RTx patients and 31% of the HD patients had a VO_2peak <20 ml/min/kg body weight. Thus, many RTx and HD patients are suffering from (physical) functional limitations in their daily life, forcing them to lead a sedentary life-style which increases the risk of cardiovascular complications.

The low VO_2peak levels of the RTx patients were remarkable. PAL appeared to be a significant predictor of VO_2peak. In healthy subjects, the relationship between PAL and VO_2peak has been established[17]. The PAL of RTx patients remains low, even after successful renal transplantation. In an earlier study, we also observed a relative low level of physical activity in RTx patients[16]. It is therefore important to establish physical exercise programs for RTx patients, in order to increase their PAL and to improve their exercise capacity.

In addition to PAL, skeletal muscle strength was a strong potential predictor of VO_2peak in RTx patients. Muscle strength is reported to be impaired in RTx patients[1,28,33]. Muscle strength of our RTx patients was also significantly lower (24%) compared to that of controls. It is becoming more evident that exercise

intolerance in renal patients is not only due to decreased oxygen delivery to the muscles during exercise. For example, correction of anemia by erythropoietin therapy leads to substantial functional benefits in HD patients, but several studies have shown that exercise intolerance persists after correction of anemia[23,26,34,35] and that other factors besides anemia limit exercise tolerance both in RTx and HD patients[22,24,36,37]. Disregarding its etiology, skeletal muscle dysfunction has been shown to be an important contributor to exercise intolerance in RTx and HD patients, and also in other chronic diseases such as COPD and congestive heart failure[22,38-40].

Skeletal muscle strength of the RTx patients appeared to be significantly and positively related to LBM. Furthermore, renal function turned out to be a significant predictor of LBM, and via LBM, of muscle strength and exercise capacity. The relationship between LBM and renal function in RTx patients has to the best of our knowledge not been described in earlier studies. The mechanisms remain to be elucidated. Possibly, in analogy to chronic renal failure, also in RTx patients a reduced protein intake may play a role[41]. Furthermore, metabolic acidosis might be involved in muscle protein degradation and consequently in the loss of muscle mass[5,42]. Unfortunately, data regarding metabolic acidosis were lacking in our study. In addition, systemic inflammation might be involved in muscle wasting[43-45]. However, in the present study no relation between inflammation and renal function or LBM was observed. Resistance to anabolic hormones is another factor which may play a role in skeletal muscle wasting[5]. In chronic renal disease, both metabolic acidosis, inflammation, and resistance to anabolic hormones, stimulate protein breakdown in muscle by activating a common proteolytic pathway, the ubiquitin-proteasome pathway[5,46]. Moreover, Adey et al.[47] described decreased synthesis rates of several muscle proteins and muscle contractile proteins as a possible basis of muscle loss and muscle weakness in patients with chronic renal failure. Besides muscle wasting, morphologic abnormalities and disturbances in aerobic and anaerobic muscle energy metabolism are described in RTx patients[1,48-52]; however, results are conflicting and further research is required to get more insight into this field.

The use of corticosteroids did not have any effect on LBM, muscle strength or exercise capacity. In an earlier cross-sectional study[16], we also found no differences in body composition (in particular in fat-free mass (FFM)) between RTx patients using different doses of steroids (0 mg, 5 mg and 10 mg prednisolone per day); moreover, no relationship was observed between the cumulative dose of steroids and body composition. Painter et al.[29] also reported no differences in body composition between RTx patients using and not using steroids, but they did observe significantly larger gains of VO_2peak and

quadriceps strength in their steroid withdrawal group compared to their steroid group in the first year after transplantation. The results of these studies were, however, difficult to compare, as Painter et al.[29] studied patients earlier after transplantation.

Major limitations of the present study are its cross-sectional design, and inherent in this design the lacking of pre-transplant and pre-dialysis data, the relative small number of patients included, the unequal numbers of males and females in the HD group (a problem which was, however, solved by correcting for gender in the ANOVA-analyses) and the wide range in post-transplantation time and time since starting hemodialysis. Regarding the last, it would have been more appropriate if patients had been tested at a same post-transplantation time or at a same time since starting hemodialysis. However, no relationships were observed between the post-transplantation time or time since starting hemodialysis and LBM, muscle strength, and exercise capacity. Moreover, post-transplantation time did not have any significant effect in the multivariate analyses. Finally, we should acknowledge that several interrelated factors, such as greater anemia in the HD group and increased FM in the RTx group may have affected the results.

Future, larger, longitudinal studies - for RTx patients starting pre-transplant with follow-up at the post-transplant period, and for HD patients starting pre-dialysis with follow-up at the dialysis period (obviously, preferably starting pre-dialysis with follow-up at the dialysis and post-transplant period) - are necessary to get more insight in the decreased skeletal muscle strength and exercise capacity of RTx and HD patients and to identify RTx patients with a poor physical exercise tolerance.

Conclusions

Exercise capacity and skeletal muscle strength of the RTx patients were significantly lower compared to age-matched, healthy controls, but not significantly different compared to HD patients. Muscle strength and PAL appeared to be highly related to exercise capacity in RTx patients. Moreover, muscle strength itself was strongly related to LBM. Renal function turned out to be a significant predictor of LBM, and subsequently of muscle strength and exercise capacity, while no effects of the use of corticosteroids were observed. Regular physical activity thus appears to be an important determinant of exercise capacity in RTx patients. The present study therefore underscores the clinical importance of rehabilitation and physical exercise programs in RTx patients.

References

1. Kempeneers G, Noakes TD, van Zyl-Smit R, Myburgh KH, Lambert M, Adams B, Wiggins T. Skeletal muscle limits the exercise tolerance of renal transplant recipients: effects of a graded exercise training program. Am J Kidney Dis 1990; 16(1):57-65.
2. Painter P, Hanson P, Messer-Rehak D, Zimmerman SW, Glass NR. Exercise tolerance changes following renal transplantation. Am J Kidney Dis 1987; 10(6):452-456.
3. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis 2003; 42(5):864-881.
4. Kopple JD. Nutritional status as a predictor of morbidity and mortality in maintenance dialysis patients. ASAIO J 1997; 43(3):246-250.
5. Mitch WE. Insights into the abnormalities of chronic renal disease attributed to malnutrition. J Am Soc Nephrol 2002; 13(Suppl 1):S22-27.
6. Mitch WE, Medina R, Grieber S, May RC, England BK, Price SR, Bailey JL, Goldberg AL. Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. J Clin Invest 1994; 93(5):2127-2133.
7. Moore LW, Gaber, OA. Patterns of early weight change after renal transplantation. J Ren Nutr 1996; 6(1):21-25.
8. Verran D, Munn S, Collins J, Hill G. Impact of renal allograft implantation and immunosuppression on body composition using in vivo neutron activation analysis. Transplant Proc 1992; 24(1):173-174.
9. Gonyea JE, Anderson CF. Weight change and serum lipoproteins in recipients of renal allografts. Mayo Clin Proc 1992; 67(7):653-657.
10. van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP. Posttransplantation weight gain is predominantly due to an increase in body fat mass. Transplantation 2000; 70(1):241-242.
11. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger P, Horber FF. Body composition and fuel metabolism after kidney grafting. Eur J Clin Invest 1995; 25(11):809-816.
12. Isiklar I, Akin O, Demirag A, Niron EA. Effects of renal transplantation on body composition. Transplant Proc 1998; 30(3):831-832.
13. Booth FW, Gollnick PD. Effects of disuse on the structure and function of skeletal muscle. Med Sci Sports Exerc 1983; 15(5):415-420.
14. Coyle EF, Martin WH, Bloomfield SA, Lowry OH, Holloszy JO. Effects of detraining on responses to submaximal exercise. J Appl Physiol 1985; 59(3):853-859.
15. Larsson L, Ansved T. Effects of long-term physical training and detraining on enzyme histochemical and functional skeletal muscle characteristic in man. Muscle Nerve 1985; 8(8):714-722.
16. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation 2000; 69(8):1591-1598.
17. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Lippincott Williams and Wilkins, Baltimore. 1999.
18. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry. J Am Soc Nephrol 1999; 10(5):1067-1079.
19. Rothkrantz-Kos S, Bekers O, Gubbels A, Drent M, Schmitz MP, van Dieijen-Visser MP. Evaluation of two new high-sensitivity methods for C-reactive protein. Ann Clin Biochem 2003; 40(Pt 4):398-405.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.

21. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982; 36(5):936-942.
22. Diesel W, Noakes TD, Swanepoel C, Lambert M. Isokinetic muscle strength predicts maximum exercise tolerance in renal patients on chronic hemodialysis. Am J Kidney Dis 1990; 16(2):109-114.
23. Lundin AP, Akerman MJ, Chesler RM, Delano BG, Goldberg N, Stein RA, Friedman EA. Exercise in hemodialysis patients after treatment with recombinant human erythropoietin. Nephron 1991; 58(3):315-319.
24. Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH. Uremic myopathy limits aerobic capacity in hemodialysis patients. Am J Kidney Dis 1993; 22(2):277-287.
25. Sietsema KE, Hiatt WR, Esler A, Adler S, Amato A, Brass EP. Clinical and demographic predictors of exercise capacity in end-stage renal disease. Am J Kidney Dis 2002; 39(1):76-85.
26. Painter P, Moore G, Carlson L, Paul S, Myll J, Phillips W, Haskell W. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. Am J Kidney Dis 2002; 39(2):257-265.
27. Painter P, Messer-Rehak D, Hanson P, Zimmerman SW, Glass NR. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron 1986; 42(1):47-51.
28. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL. A randomized trial of exercise training after renal transplantation. Transplantation 2002; 74(1): 42-48.
29. Painter PL, Topp KS, Krasnoff JB, Adey D, Strasner A, Tomlanovich S, Stock P. Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients. Kidney Int 2003; 63(6):2309-2316.
30. Violan MA, Pomes T, Maldonado S, Roura G, De la Fuente I, Verdaguer T, Lloret R, Torregrosa JV, Campistol JM. Exercise capacity in hemodialysis and renal transplant patients. Transplant Proc 2002; 34(1):417-418.
31. Kettner A, Goldberg A, Hagberg J, Delmez J, Harter H. Cardiovascular and metabolic responses to submaximal exercise in hemodialysis patients. Kidney Int 1984; 26(1):66-71.
32. Janicki JS, Weber KT, McElroy PA. Use of the cardiopulmonary exercise test to evaluate the patient with chronic heart failure. Eur Heart J 1988; 9(Suppl H):55-58.
33. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. Kidney Int 2003; 63(1):291-297.
34. Metra M, Cannella G, La Canna G, Guaini T, Sandrini M, Gaggiotti M, Movilli E, Dei Cas L. Improvement in exercise capacity after correction of anemia in patients with end-stage renal failure. Am J Cardiol 1991; 68(10):1060-1066.
35. Johansen KL. Physical functioning and exercise capacity in patients on dialysis. Adv Ren Replace Ther 1999; 6(2):141-148.
36. Marrades RM, Roca J, Campistol JM, Diaz O, Barbera JA, Torregrosa JV, Masclans JR, Cobos A, Rodriguez-Roisin R, Wagner PD. Effects of erythropoietin on muscle O_2 transport during exercise in patients with chronic renal failure. J Clin Invest 1996; 97(9):2092-2100.
37. Moore GE, Bertocci LA, Painter PL. 31P-magnetic resonance spectroscopy assessment of subnormal oxidative metabolism in skeletal muscle of renal failure patients. J Clin Invest 1993; 91(2):420-424.
38. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 1996; 153(3):976-980.
39. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation 1992; 85(5):1751-1759.
40. Magnusson G, Kaijser L, Rong H, Isberg B, Sylven C, Saltin B. Exercise capacity in heart failure patients: relative importance of heart and skeletal muscle. Clin Physiol 1996; 16(2): 183-195.

41. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int 2000; 57(4):1688-1703.
42. Graham KA, Reaich D, Channon SM, Downie S, Goodship TH. Correction of acidosis in hemodialysis decreases whole-body protein degradation. J Am Soc Nephrol 1997; 8(4): 632-637.
43. Laville M, Fouque D. Nutritional aspects in hemodialysis. Kidney Int Suppl 2000; 76: S133-139.
44. Kaizu Y, Ohkawa S, Odamaki M, Ikegaya N, Hibi I, Miyaji K, Kumagai H. Association between inflammatory mediators and muscle mass in long-term hemodialysis patients. Am J Kidney Dis 2003; 42(2):295-302.
45. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. Semin Dial 2002; 15(5):329-337.
46. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. N Engl J Med 1996; 335(25):1897-1905.
47. Adey D, Kumar R, McCarthy JT, Nair KS. Reduced synthesis of muscle proteins in chronic renal failure. Am J Physiol Endocrinol Metab 2000; 278(2):E219-225.
48. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Tourkantonis A, Deligiannis A. The effects of exercise training on muscle atrophy in haemodialysis patients. Nephrol Dial Transplant 1998; 13(3):685-699.
49. Fahal IH, Bell GM, Bone JM, Edwards RH. Physiological abnormalities of skeletal muscle in dialysis patients. Nephrol Dial Transplant 1997; 12(1):119-127.
50. Diesel W, Emms M, Knight BK, Noakes TD, Swanepoel CR, van Zyl Smit R, Kaschula RO, Sinclair-Smith CC. Morphologic features of the myopathy associated with chronic renal failure. Am J Kidney Dis 1993; 22(5):677-684.
51. Horber FF, Hoppeler H, Herren D, Claassen H, Howald H, Gerber C, Frey FJ. Altered skeletal muscle ultrastructure in renal transplant patients on prednisone. Kidney Int 1986; 30(3):411-416.
52. Topp KS, Painter PL, Walcott S, Krasnoff JB, Adey D, Sakkas GK, Taylor J, McCormick K, te Nyenhuis M, Iofina M, Tomlanovich S, Stock P. Alterations in skeletal muscle structure are minimized with steroid withdrawal after renal transplantation. Transplantation 2003; 76(4):667-673.

Chapter 8

Comparison of the response to exercise training in renal transplant patients, hemodialysis patients, and healthy controls

ECH van den Ham, JP Kooman, AMWJ Schols, FHM Nieman, JD Does, MA Akkermans, PP Janssen, MHL Christiaans, KML Leunissen, JP van Hooff

Submitted

Abstract

Background
The use of corticosteroids and the presence of catabolic factors could impair the response to exercise training in renal transplant and hemodialysis patients, respectively. We assessed and compared the response to training in renal transplant patients, hemodialysis patients, and healthy controls, and investigated the effects of low-dose corticosteroids on this response in renal transplant patients.

Subjects and methods
Exercise capacity, muscle strength, lean body mass and quality of life were measured by cycle-ergometry, dynamometry, fitness equipment, dual energy x-ray absorptiometry, and SF-36 in 33 renal transplant patients, 14 hemodialysis patients and 18 controls before and after a twelve-weeks lasting supervised training program.

Results
VO_2peak and muscle strength improved significantly over the training period in both patients and controls ($p_{time}<0.05$). Changes in exercise capacity and strength were not different between the three groups. Male controls had significantly higher gains of lean body mass than renal transplant ($p<0.05$) and hemodialysis patients ($p<0.05$), in which lean body mass remained about constant. Quality of life improved in renal transplant and hemodialysis patients. No effects of corticosteroids were observed.

Conclusions
The functional response to training did not differ between renal transplant patients, hemodialysis patients, and controls. The anabolic response appeared to be different between patients and controls. Exercise training improves quality of life in renal patients. This study underscores the clinical importance of exercise training in renal patients.

Introduction

Exercise intolerance is common in hemodialysis (HD)[1-5] patients and severely compromises quality of life (QoL). Potential factors influencing exercise capacity in HD patients are factors related to the uremic state or the dialysis treatment itself, skeletal muscle wasting and weakness, and physical inactivity.
Successful transplantation corrects or improves many of the systemic abnormalities influencing exercise capacity in HD patients. Although exercise capacity appears to improve spontaneously after renal transplantation[6], we recently showed that exercise capacity and skeletal muscle strength of renal transplant (RTx) patients were significantly reduced compared to healthy controls, and not significantly different compared to HD patients on the transplant waiting list[7]. Moreover, we found skeletal muscle strength and physical activity level to be important determinants of exercise capacity in RTx patients[7].
Previous studies showed that exercise training leads to an improvement in exercise capacity, muscle strength, and QoL in RTx and HD patients[1,8-16]. RTx recipients are mostly using corticosteroids and often have a suboptimal renal function. Therefore, the response to exercise training might be lower compared to healthy individuals. The response to training may even be lower in HD patients, due to the presence of multiple catabolic factors. To the best of our knowledge, the response to standardized exercise training has not yet been compared between RTx patients, HD patients, and healthy controls.
We hypothesize that exercise capacity, muscle strength, and QoL improve after exercise training in RTx and HD patients, but that the functional response in RTx patients is less compared to healthy controls and higher compared to HD patients. The primary aim of the study was to assess and compare the response to intensive, supervised, standardized exercise training on exercise capacity, muscle strength, body composition, and QoL in RTx patients, HD patients, and controls. Next to this, we wished to investigate whether differences in response to training exist between RTx patients using or not using steroids.

Subjects and methods

Subjects

RTx patients, HD patients, and age-matched, sedentary, healthy controls (aged 21-71 years) were included in the study. Inclusion and exclusion criteria are summarized in table 8.1.

Table 8.1 Inclusion and exclusion criteria for the study

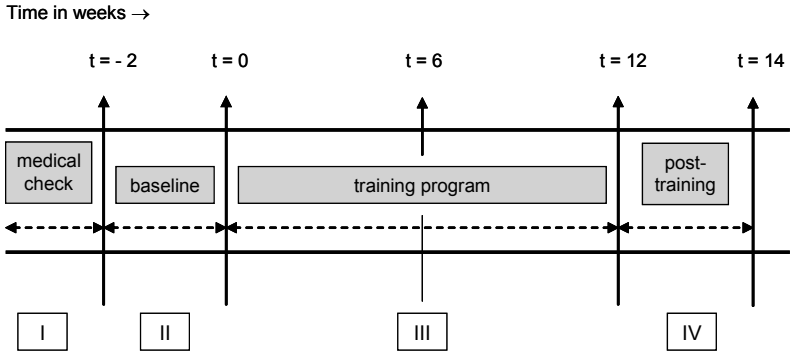
Inclusion criteria:	RTx patients:	- transplantation at least six months before start of the study
	HD patients:	- on the waiting list for renal transplantation - thrice weekly dialysis therapy - use of synthetic or modified cellulose membranes - double pool Kt/V of 1.2 or higher
Exclusion criteria:		- hemoglobin level below 6.3 mmol/l - diabetes mellitus - history of heart disease - organ transplant other than kidney - use of corticosteroids for other reasons than kidney transplantation - musculoskeletal problems - (history of) malignancy (except non-metastatic basal or squamous cell carcinoma of the skin)

Patients who were eligible were asked to participate in the study at the outpatients' clinic of our hospital and at six hemodialysis departments in our district. Controls were either partners of patients or volunteers recruited by advertisement.
Written informed consent was obtained from each subject prior to participation. The Ethical Committee of the Maastricht University Hospital approved the study.

Methods

Study-design

The design (line-out given in figure 8.1) can be described as a natural groups cohort study in which differences between a 'before' state without stimulus are compared to the stimulus-induced 'after' state in the three groups as a whole, while at the same time response differences in time are compared between the three groups. All subjects underwent extensive medical examination and baseline measurements before training was started; renal patients also underwent exercise electrocardiography. Both the renal patients and controls participated in the training program. Exercise capacity and muscle function tests were measured again after six weeks of training; if necessary, the training intensity was adjusted (according to pre-fixed rules) in order to maintain a constant relative training intensity. All measurements performed at baseline were repeated after completion of the training program.
In HD patients, measurements (except blood sampling) were performed each time on the first nondialysis day after dialysis treatment. Training was performed on nondialysis days.



I medical examination;
II exercise electrocardiography (in renal patients) and baseline measurements of exercise capacity, skeletal muscle function, body composition, blood parameters, physical activity level, quality of life;
III follow-up measurements of exercise capacity and skeletal muscle function;
IV post-training measurements of exercise capacity, skeletal muscle function, body composition, blood parameters, physical activity level, quality of life.

Figure 8.1 Design of the study.

Exercise capacity

Maximal exercise capacity was measured by symptom-limited graded cycle-ergometry, as described previously[7]. In short, a progressively increasing work rate test was started to determine peak work rate (Wpeak) and peak oxygen uptake (VO_2peak), important indicators of exercise capacity. The work rate was increased with 10 to 25 W/min in renal patients and with 10 to 30 W/min in controls, so that the length of the test was comparable for all subjects. The test was terminated when subjects complained of limiting fatigue, dyspnea, or if electrocardiogram changes or hypertension occurred.
VO_2peak was defined as the highest recorded oxygen uptake at peak exercise and was expressed in absolute terms and relative to body weight (BW) and muscle mass (i.e., ml O_2/min/kg).

Skeletal muscle function

Isokinetic quadriceps strength of the dominant leg was measured using a Cybex II plus dynamometer (Lumex Inc., Ronkonkoma, NY), as described previously[7]. Maximal strength was defined as the highest peak torque of fifteen consecutive maximal contractions (angle velocity 90°/sec) and was expressed in absolute terms and relative to muscle mass of the legs.

Moreover, maximal strength of different muscle groups in the arms, legs, abdomen, shoulder, back, and chest was measured with specific fitness equipment.

Body composition

Whole-body composition, i.e., fat mass (FM), lean body mass (LBM, comprising muscle, inner organs and body water) and bone mineral content was measured by dual energy x-ray absorptiometry (DEXA; DPX-L, Lunar Radiation Corp., Madison, WI)[7,17]. LBM was used as an estimate of muscle mass. The extra-cellular water (ECW) volume was determined by multi-frequency bio-electrical impedance analysis (Xitron 4000B, Xitron Technologies Inc., San Diego, CA)[17].

Blood parameters

Blood samples were taken in both renal patients and controls (in HD patients just before start of dialysis treatment). All blood tests, except CRP (high-sensitivity particle-enhanced immunonephelometry[18]), were performed according to standard laboratory procedures.

Renal function

Creatinine clearance in RTx patients and controls was estimated by the Cockcroft and Gault formula[19]. In RTx patients, creatinine clearance was also calculated from 24-hr urine volume and creatinine levels in plasma and 24-hr urine.

Physical activity level

The habitual physical activity level was assessed by the Baecke questionnaire[20], as described previously[7].

Quality of life

QoL was assessed by the Medical Outcome Study Short-form 36-item (SF-36) questionnaire, which consists of 36 items categorized 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). Each scale score ranges from 0 to 100, with a higher score indicating a better health state[21,22]. Normalized scores representing overall physical and mental functioning were calculated from the individual scales and were presented as the physical component scale (PCS) and the mental component scale (MCS). The component scale scores are normalized to a general population mean of 50 and a SD of 10[23].

Exercise training program

The standardized, twelve-weeks lasting training program consisted of a combination of endurance and strength training. Subjects attended two supervised sessions a week. Each session consisted of endurance training (cycle-ergometry and treadmill walking), dynamic strength training of specific muscle groups (fitness equipment), and alternating swimming or gymnastics. The strength training was composed of once a week specific resistance training (a small number of repetitions with a relatively high load) and once a week strength-endurance training (a large number of repetitions with a relatively low load). The duration of the exercise sessions was gradually built up to two hours. Training sessions were performed in mixed groups ($n \approx 10$) of renal patients and controls.

An individual (standardized) program based on the results of the cycle and strength tests at baseline was developed for each subject. In the first six weeks of the training program, the intensity of the cycle training gradually increased from 50% to 70% of Wpeak at baseline, the intensity of the specific resistance training from 2x8 repetitions at 50% to 3x10 repetitions at 60% of the maximal strength at baseline ($Pmax_{baseline}$), and the intensity of the strength-endurance training from 1x30 repetitions at 25% to 3x30 repetitions at 35% of $Pmax_{baseline}$. In weeks 7 till 12, the intensity of the cycle training increased from 60% of Wpeak measured after six weeks of training ($Wpeak_{six}$) to finally 70% of $Wpeak_{six}$, the intensity of the resistance training from 2x10 repetitions at 50% to 3x10 repetitions at 60% of $Pmax_{six}$, and the intensity of the strength-endurance training from 1x30 repetitions at 25% to 3x30 repetitions at 35% of $Pmax_{six}$. Treadmill walking all the time was performed just below the symptom-limited rate, at which heart rates were comparable to those reached during cycle-training.

Statistics

Patient characteristics and baseline comparisons

The Kolmogorov-Smirnov test was used to test for normal distribution of variables. Nonparametric Kruskal-Wallis tests (if necessary, followed by Mann-Whitney *U* tests) were used to compare not normally distributed variables between the groups. Approximately normally distributed variables were compared by one-way analysis of variance (ANOVA) with correction for pairwise multiple comparisons via post hoc Bonferroni or Dunnett T3 tests. Two-way analysis of variance followed by Bonferroni's or Dunnett T3's pairwise multiple comparisons procedure was used to determine gender-corrected differences between the groups. Differences in discrete variables between groups were assessed with the log-likelihood Chi-Square test.

Effects of training

In-time-changes of parameters during the training program within the total group, as well as differences in these changes between the three groups were analyzed by repeated measures AN(C)OVA. In this way, the effects of the factor 'time', 'group', and of the interaction term 'time by group' could be determined. A significant 'time' factor can be interpreted that the parameters, averaged over all groups, significantly change over the training period; a significant 'time by group' interaction term points to differences in the within-time changes of these parameters between the three groups. If a significant overall 'time by group' interaction was found, separate paired *t* tests were performed to determine changes over time for each group. Analysis of QoL was performed by testing time differences by Kruskal-Wallis test for those scales not normally distributed and untransformable to normal distributions.
Data are generally expressed as mean±SD, unless indicated otherwise. Statistical analysis was performed by SPSS for Windows, version 12.0. P-values <0.05 were considered statistically significant.

Results

Patient characteristics

Thirty-five RTx patients, 16 HD patients and 21 controls were enrolled in the study. Thirty-three RTx, 14 HD and 18 controls fully completed the training, and had complete registration of baseline and follow-up measurements. Reasons for drop-out were hospitalization for cataract surgery (1x) and personal problems (1x) in the RTx group, hospitalization for pneumonia (1x) and refusal to continue training (1x) in the HD group, and electrocardiogram abnormalities during the baseline cycle-test (2x) and overstraining (1x) in controls. Subject characteristics are given in table 8.2. Baseline comparisons of exercise capacity, muscle function and body composition are described in detail elsewhere[7].

Table 8.2 Subject characteristics at baseline

	RTx (n=33)	HD (n=14)	Controls (n=18)
Age (yr)	52.1 ± 10.3	48.4 ± 11.9	55.7 ± 10.0
Gender (M/F)	18/15	9/5	9/9
Body weight (kg)	74.6 ± 15.1	67.9 ± 14.1[i]	79.6 ± 12.3
BMI (kg/m^2)	25.7 ± 3.9	23.1 ± 3.5[j]	26.5 ± 2.9
Time after Tx (months)	86.2 ± 82.4[f]	-	-
Time on dialysis prior to Tx (months)	24.9 ± 20.5[g]	-	-
Time on dialysis (months)	-	22.4 ± 15.7[h]	-
Creatinine clearance (ml/min)[a]	59.7 ± 16.3[m]	-	103.0 ± 22.2
Creatinine clearance (ml/min)[b]	62.9 ± 18.7		
Smoking	4 (12.1%)	5 (35.7%)	4 (22.2%)
Blood parameters			
Hemoglobin (mmol/l)	8.6 ± 1.0	7.6 ± 0.7[kl]	8.8 ± 0.8
Creatinine (μmol/l)[c]	136 ± 52[m]	1012 ± 378[mo]	75 ± 12
Urea (mmol/l)	8.8 ± 4.1[j]	23.8 ± 6.8[jl]	4.5 ± 0.9
Albumin (g/l)	41.6 ± 3.3	41.0 ± 3.9	41.9 ± 2.3
Glucose (mmol/l)[c]	5.8 ± 0.9	5.5 ± 1.1	5.5 ± 0.7
CRP (mg/l)	4.0 ± 3.4	6.4 ± 10.2	3.5 ± 3.4
Sodium (mmol/l)	139.5 ± 1.7	138.0 ± 2.4[n]	-
Potassium (μmol/l)	4.5 ± 0.5	4.9 ± 0.7[n]	-
Calcium (mmol/l)	2.43 ± 0.16	2.32 ± 0.20[p]	-
Phosphate (mmol/l)	1.08 ± 0.32	1.81 ± 0.60[o]	-
PTH (mmol/l)	9.9 ± 4.5	15.8 ± 10.1[q]	-
Causes of renal failure			
Chronic glomerulonephritis	16 (48.5%)	6 (42.9%)	-
Pyelonephritis / interstitial nephritis	3 (9.1%)	1 (7.1%)	-
Nephrosclerosis	3 (9.1%)	2 (14.3%)	-
Polycystic kidney disease	7 (21.2%)	3 (21.4%)	-
Congenital sphincter sclerosis	1 (3.0%)	-	-
Unknown	3 (9.1%)	2 (14.3%)	-
Medication use			
Steroid-based immunosuppression[d]	16 (48.6%)	-	-
Steroid-free immunosuppression[e]	17 (51.4%)	-	-
β-blockers	23 (69.7%)	6 (42.9%)	-
Erythropoetin	-	13 (92.9%)	-
Physical activity level			
Occupational activity index	2.3 ± 0.9	1.9 ± 1.0	2.6 ± 0.7
Sport activity index	2.2 ± 0.8	1.8 ± 0.6[r]	2.5 ± 0.8
Leisure time activity index	2.6 ± 0.6	2.5 ± 0.7	2.7 ± 0.5
Total activity index	7.2 ± 1.5	6.2 ± 1.5[j]	7.8 ± 1.5

Data given as mean ± SD or as number of patients (% of patients); [a] calculated by Cockcroft and Gault formula; [b] calculated from 24-hr urine volume and creatinine levels in plasma and 24-hr urine; [c] data not normally distributed; [d] prednisolone (5-10 mg/day) in combination with FK-506 or Cyclosporin-A; [e] FK-506 or Cyclosporin-A mono-therapy; [f] median time after Tx=46.9 months (range: 8.7-289.3 months); [g] median time on dialysis prior to Tx (n=31; two patients pre-emptive RTx)=19.6 months (range: 0.7-84.0 months); [h] median time on dialysis=17.1 months (range: 3.0-56.3 months); [i] p=0.059 versus controls, corrected for gender; [j] p<0.05 versus controls, corrected for gender; [k] p<0.01 versus controls, corrected for gender; [l] p<0.01 versus RTx, corrected for gender; [m] p<0.01 versus controls ; [n] p<0.05 versus RTx; [o] p<0.01 versus RTx; [p] p=0.058 versus RTx; [q] p=0.056 versus RTx ; [r] p=0.053 versus controls, corrected for gender; BMI=body mass index; Tx=transplantation; CRP=C-reactive protein; PTH=parathyroid hormone.

Response to exercise training: comparison of the groups

Exercise capacity

Wpeak of both patients and controls improved over the training period (p_{time}<0.001). VO_2peak (absolute and adjusted for BW and LBM) also increased ($p_{time}\leq$0.01), just like the respiratory exchange ratio at Wpeak (p_{time}<0.05). There were no significant differences in the changes of Wpeak, VO_2peak, and the respiratory exchange ratio over time between the RTx, HD, or control group (figure 8.2). Changes of exercise capacity over time adjusted for age and gender were not significantly different between groups either (table 8.3).

Skeletal muscle function

Quadriceps strength (absolute and adjusted for lean mass (LM) of the legs) increased significantly over time in both patients and controls (p_{time}<0.001 and p_{time}<0.05, respectively). The change of quadriceps strength over time was not significantly different between the three groups (figure 8.2), also not, if corrected for age and gender (table 8.3).

The maximal strength of the different muscle groups in the arms, legs, abdomen, shoulder, back, and chest also improved significantly over time in both patients and controls (p_{time}<0.05). Changes in strength of these muscle groups over time were not significantly different between the three groups (figure 8.2, table 8.3; results not all shown).

Body composition

Because of a significant interaction between 'gender' and 'group' in the statistical analyses, separate analyses were performed for males and females.

In *males*, BW did not change significantly over time in patients and controls, but the LBM increased significantly (p_{time}=0.028; figure 8.3). Changes of BW and LBM over time were significantly different among the RTx, HD, and control group, also after adjustment for age (p_{group}<0.001 and p_{group}=0.027, respectively; table 8.4). Controls had significantly higher gains of BW and LBM than RTx (p=0.001 and p<0.05, respectively) or HD patients (p<0.001 and p<0.05, respectively). BW actually decreased in both RTx and HD patients, while LBM remained about constant. Changes of BW and LBM were not significantly different between the patient groups. FM and percentage of body fat did just not significantly change over time in both male patients and controls (p_{time}=0.09 and p_{time}=0.052, respectively) nor ECW did change significantly; moreover, changes in these parameters over time were not significantly different between the groups (table 8.4).

In the total group of *female* patients and controls, BW, body mass index (BMI), LBM, FM, percentage of body fat and ECW did not change significantly over

time. Changes in these parameters over the training period were also not significantly different between the groups.

Table 8.3 Changes in exercise capacity and skeletal muscle strenght in the RTx, HD, and control group (results of regression analysis, adjusted for age and gender)

	RTx (n=33)	HD (n=14)	Controls (n=18)	F-ratio 'group' [a]
Exercise capacity				
Wpeak (Watt)				
baseline	135 ± 50	118 ± 54	179 ± 57	
post-training	162 ± 60	145 ± 66	210 ± 68	$F_{(2,59)}$ =1.245; p=0.295
VO_2peak (ml/min)				
baseline	1600 ± 567	1539 ± 747	2222 ± 786	
post-training	1747 ± 515	1668 ± 702	2279 ± 876	$F_{(2,58)}$ =0.261; p=0.771
VO_2peak (ml/min/kg BW)				
baseline	21.6 ± 6.3	21.8 ± 7.8	27.5 ± 7.6	
post-training	23.8 ± 6.1	23.9 ± 7.4	28.0 ± 8.2	$F_{(2,58)}$ =0.870; p=0.425
VO_2peak (ml/min/kg LBM)				
baseline	33.3 ± 8.1	31.5 ± 9.4	42.6 ± 9.6	
post-training	36.9 ± 7.9	34.2 ± 8.4	42.6 ± 10.0	$F_{(2,58)}$ =1.707; p=0.190
RER-peak				
baseline	1.15 ± 0.08	1.15 ± 0.11	1.16 ± 0.09	
post-training	1.19 ± 0.10	1.21 ± 0.10	1.15 ± 0.08	$F_{(2,58)}$ =1.499; p=0.232
Skeletal muscle strength				
Quadriceps (nM)[b]				
baseline	89.6 ± 31.2	86.4 ± 30.7	122.6 ± 34.7	
post-training	98.8 ± 33.2	89.0 ± 34.1	133.6 ± 42.0	$F_{(2,52)}$ =1.293; p=0.283
Quadriceps (nM/kg LM legs)[b]				
baseline	5.7 ± 1.3	5.6 ± 1.2	7.0 ± 1.1	
post-training	6.3 ± 1.2	5.7 ± 1.5	7.4 ± 1.2	$F_{(2,52)}$ =1.057; p=0.355
Arms / back (kg)[c]				
baseline	38.5 ± 11.8	36.9 ± 12.9	45.6 ± 14.7	
post-training	47.1 ± 15.2	45.9 ± 15.9	54.1 ± 16.4	$F_{(2,57)}$ =0.046; p=0.955
Chest (kg)[d]				
baseline	33.6 ± 13.7	31.7 ± 14.6	39.3 ± 14.6	
post-training	47.0 ± 18.2	44.7 ± 18.3	53.8 ± 19.3	$F_{(2,59)}$ =0.836; p=0.438
Shoulder / back (kg)[e]				
baseline	24.8 ± 10.5	24.8 ± 11.2	31.0 ± 11.2	
post-training	31.5 ± 12.8	33.3 ± 13.6	38.6 ± 12.0	$F_{(2,56)}$ =0.570; p=0.569
Abdomen (kg)[f]				
baseline	33.6 ± 13.5	30.5 ± 13.3	39.1 ± 14.1	
post-training	41.7 ± 15.2	41.1 ± 15.9	50.2 ± 15.3	$F_{(2,58)}$ =2.742; p=0.073

Data given as mean ± SD; [a] F-ratio=F-ratio of the effects of 'group'; [b] quadriceps strength measured by Cybex; [c] biceps brachii, latissimus dorsi, and terres major; [d] pectoralis major and deltoideus anterior; [e] trapezius, deltoideus anterior, and subscapularis; [f] obliquus externus, obliquus internus, and rectus abdominus; W=work load; VO_2=oxygen uptake; BW=body weight; LBM=lean body mass; RER=respiratory exchange ratio; LM=lean mass.

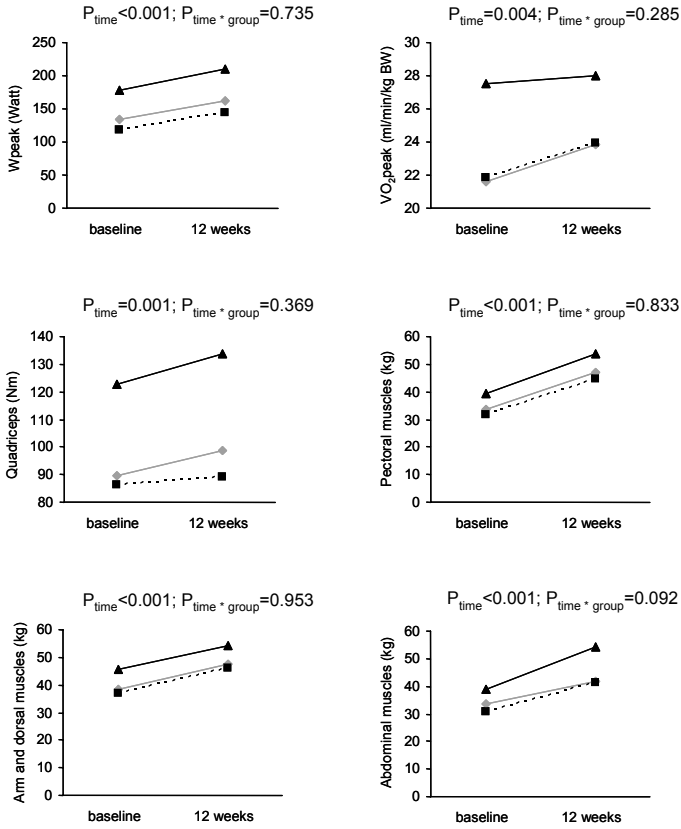


Figure 8.2 Changes of exercise capacity and skeletal muscle strength in the RTx, HD, and control group from baseline to 12 weeks of training (non-adjusted for age and gender). Results of the two-way repeated measures ANOVA. Wpeak=peak work rate; VO_2=peak oxygen uptake; BW=body weight; —◆— RTx; ···■··· HD; —▲— control.

Quality of life

The PF, RP, GH, VT, and MCS scores of both patients and controls significantly improved over the training period (p_{time}<0.05); the improvement of the PCS was just not significant (p_{time}=0.076; figure 8.4). Only changes in PF and VT scores over time were significantly different between the three groups (p_{group}<0.01 and p_{group}<0.05, respectively; table 8.5). The increase in the PF score in the RTx and HD group was significantly larger compared to that in controls (p<0.001 and p<0.05, respectively), but was not different between the patient groups. The change in the VT score in RTx patients was not significantly different compared to the change in controls. The lower increase of this score in RTx patients compared to HD patients was just not significant (p=0.056). The increase in the VT score in HD patients was, however, significantly larger compared to that in controls (p<0.01).

Table 8.4 Changes in body composition in the RTx, HD, and control group (results of regression analysis, adjusted for age)

	Males				Females			
	RTx (n=18)	HD (n=9)	Controls (n=9)	F-ratio 'group' [a]	RTx (n=15)	HD (n=5)	Controls (n=9)	F-ratio 'group' [a]
Body weight (kg)								
baseline	77.8±10.5	74.0±12.6	86.9±6.5		70.7±18.9	56.9±9.5	72.3±12.6	
post-training	77.5±10.5	73.3±12.1[b]	88.8±8.0[c]	$F_{(2,32)}$=10.008; p<0.001	70.7±19.4	57.8±9.8	72.1±12.3	$F_{(2,25)}$=1.019; p=0.375
BMI (kg/m^2)								
baseline	25.5±2.5	23.7±3.5	26.4±1.6		25.9±5.2	21.9±3.7	26.6±3.9	
post-training	25.4±2.5	23.5±3.3[b]	27.0±1.9[d]	$F_{(2,32)}$=9.978; p<0.001	25.8±5.4	22.3±3.7	26.5±3.9	$F_{(2,25)}$=1.093; p=0.351
LBM (kg)								
baseline	54.0±8.2	53.8±8.6	62.2±3.3		40.7±6.2	34.9±5.9	41.1±6.7	
post-training	54.2±8.2	53.7±8.7	64.5±4.4[e]	$F_{(2,32)}$=4.072; p=0.027	39.9±6.8	36.0±6.1	41.5±6.6	$F_{(2,25)}$=2.871; p=0.075
FM (kg)								
baseline	21.0±4.3	17.4±4.7	21.2±3.6		27.7±13.6	19.9±5.3	28.6±6.9	
post-training	20.5±4.0	16.8±4.3	20.8±4.3	$F_{(2,32)}$=0.258; p=0.774	28.5±14.0	19.6±9.4	28.0±6.7	$F_{(2,25)}$=1.847; p=0.179
BF (% of BW)								
baseline	27.1±4.8	23.3±3.6	24.3±2.6		37.2±9.5	34.6±5.7	39.3±4.3	
post-training	26.5±4.4	22.8±3.7	23.3±3.3	$F_{(2,32)}$=0.122; p=0.885	38.3±10.3	33.4±4.5	38.5±4.5	$F_{(2,25)}$=2.185; p=0.133
ECW (l)								
baseline	22.1±2.7	20.8±2.6	24.7±1.6		17.7±2.7	15.5±2.1	17.5±2.8	
post-training	21.8±2.8	20.5±2.9	24.4±1.9	$F_{(2,32)}$=0.013; p=0.994	17.6±2.7	14.2±3.1	17.5±2.8	$F_{(2,23)}$=2.659; p=0.091

Data given as mean ± SD; [a] F-ratio=F-ratio of the effects of 'group'; [b] p<0.05 compared to baseline; [c] p=0.058 compared to baseline; [d] p=0.053 compared to baseline; [e] p<0.01 compared to baseline; BMI=body mass index; LBM=lean body mass; FM=fat mass; BF=body fat; BW=body weight; ECW=extra-cellular water.

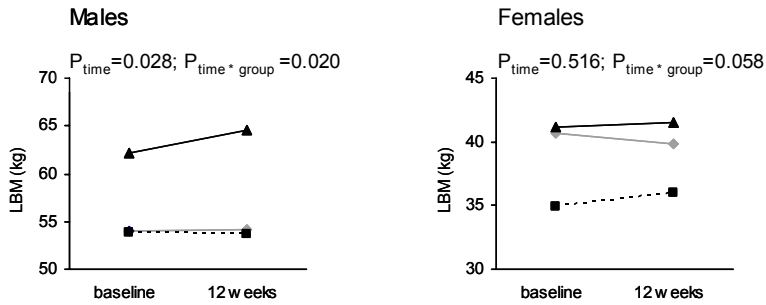


Figure 8.3 Changes in LBM in the RTx, HD, and control group from baseline to 12 weeks of training (non-adjusted for age). Results of the two-way repeated measures ANOVA. LBM=lean body mass; RTx; HD; control.

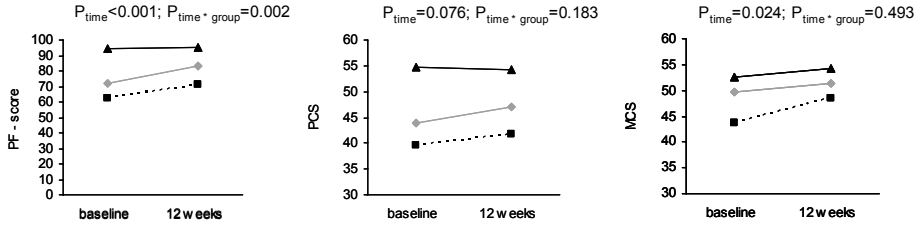


Figure 8.4 Changes in quality of life in the RTx, HD, and control group from baseline to 12 weeks of training (non-adjusted for age and gender). Results of the two-way repeated measures ANOVA. PF=physical functioning; PCS=physical component scale; MCS= mental component scale; —◆— RTx; ···■··· HD; —▲— control.

Response to exercise in the RTx group: comparison of patients with and without steroids

Sixteen RTx patients were using steroids (ST+) and 17 RTx patients were on a steroid-free regimen (ST-) during the study. Groups were comparable for age, gender and renal function. Six patients in the ST- group had been off steroids for less than one year at the moment of testing; the cumulative dosage of steroids they did receive, was, however, relatively low (on the average 1.5±0.4 g). The other 11 patients in the ST- group had been off steroids for more than one year (on the average 31.7±19.1 months).

Exercise capacity and muscle strength of the patients in both ST+ and ST- groups improved over time ($p_{time} \leq 0.01$), while no changes in body composition were observed. There appeared to be no significant differences in changes of exercise capacity, muscle strength, and body composition over time among the ST+ and ST- group (table 8.6). Also changes in QoL over the training period appeared to be not significantly different between these groups (data not shown).

Table 8.5 Changes in SF-36 scale scores in the RTx, HD, and control group (results of regression analysis, adjusted for age and gender)

	RTx (n=29)	HD (n=13)	Controls (n=17)	F-ratio 'group' [a]
Physical functioning				
baseline	71.9 ± 18.2[c]	62.3 ± 27.4[c]	94.4 ± 6.1	
post-training	83.1 ± 14.1[d]	71.5 ± 24.5[f]	95.0 ± 7.5	$F_{(2,54)}$ =6.982; p=0.002
Role functioning[b]				
baseline	63.8 ± 40.4[c]	38.5 ± 45.2[cg]	95.6 ± 18.2	
post-training	80.2 ± 35.0	53.8 ± 44.3	92.6 ± 24.6	-
Bodily pain				
baseline	74.6 ± 18.8[e]	62.8 ± 30.5[e]	88.6 ± 14.0	
post-training	75.8 ± 20.4	65.8 ± 30.0	86.9 ± 19.2	$F_{(2,54)}$ =0.192; p=0.826
General health				
baseline	50.1 ± 20.8[c]	41.2 ± 18.3[c]	77.4 ± 13.7	
post-training	52.0 ± 22.6	45.5 ± 19.0	82.8 ± 15.8	$F_{(2,52)}$ =0.456; p=0.636
Vitality				
baseline	62.9 ± 16.8[c]	49.2 ± 22.9[ch]	82.5 ± 11.5	
post-training	66.9 ± 16.6	61.9 ± 21.7[i]	80.9 ± 13.3	$F_{(2,53)}$ =4.033; p=0.023
Social functioning[b]				
baseline	81.5 ± 19.7	69.2 ± 29.6	89.0 ± 17.6	
post-training	84.3 ± 19.2	76.9 ± 22.7	90.4 ± 15.0	-
Role emotional[b]				
baseline	78.2 ± 35.9	56.4 ± 47.9	89.6 ± 23.5	
post-training	79.3 ± 37.2	69.2 ± 48.0	87.5 ± 26.9	-
Mental health				
baseline	73.8 ± 17.4[e]	65.2 ± 21.7[e]	85.8 ± 12.3	
post-training	78.1 ± 16.0	67.1 ± 17.7	85.0 ± 14.3	$F_{(2,53)}$ =0.921; p=0.404
PCS				
baseline	43.9 ± 9.0[c]	39.6 ± 11.5[c]	54.8 ± 5.2	
post-training	47.0 ± 8.9	41.8 ± 10.8	54.2 ± 5.4	$F_{(2,49)}$ =1.930; p=0.156
MCS				
baseline	49.6 ± 12.1	43.6 ± 13.2	52.6 ± 8.1	
post-training	51.3 ± 11.6	48.5 ± 11.1	54.3 ± 8.6	$F_{(2,49)}$ =0.398; p=0.674

Data given as mean ± SD; [a] F-ratio=F-ratio of the effects of 'group'; [b] baseline data and 'difference between the scores at baseline and after 12 weeks of training' not normally distributed; Kruskall-Wallis test over 'the difference between the scores at baseline and after 12 weeks of training' statistically not significant; [c] p<0.01 compared to baseline score of controls; [d] p<0.001 compared to baseline; [e] p<0.05 compared to baseline score of controls; [f] p<0.05 compared to baseline; [g] p=0.098 compared to baseline scores of RTx patients; [h] p=0.060 compared to baseline scores of RTx patients; [i] p=0.055 compared to baseline; PCS=physical component scale; MCS=mental component scale.

Table 8.6 Changes in exercise capacity, skeletal muscle strength, and body composition in RTx patients on steroid-based and steroid-free immunosuppression (results of regression analysis, adjusted for age and gender)

	ST+ (n=16)	ST- (n=17)	F-ratio 'steroid group' [a]
Exercise capacity			
Wpeak (Watt)			
baseline	136 ± 52	134 ± 51	
post-training	158 ± 55	166 ± 66	$F_{(1,28)}$ =2.534; p=0.123
VO_2peak (ml/min)			
baseline	1584 ± 616	1616 ± 534	
post-training	1638 ± 426	1855 ± 584	$F_{(1,28)}$ =2.791; p=0.106
VO_2peak (ml/min/kg BW)			
baseline	21.3 ± 6.4	21.9 ± 6.3	
post-training	22.5 ± 5.8	25.1 ± 6.4	$F_{(1,28)}$ =1.938; p=0.175
VO_2peak (ml/min/kg LBM)			
baseline	32.8 ± 8.3	33.8 ± 9.0	
post-training	35.1 ± 7.2	38.7 ± 8.4	$F_{(1,28)}$ =1.097; p=0.304
RER-peak			
baseline	1.16 ± 0.07	1.14 ± 0.09	
post-training	1.18 ± 0.09	1.19 ± 0.11	$F_{(1,28)}$ =0.587; p=0.450
Skeletal muscle strength			
Quadriceps (nM)			
baseline	85.3 ± 28.0	93.0 ± 34.0	
post-training	98.3 ± 34.2	99.2 ± 33.4	$F_{(1,27)}$ =1.223; p=0.279
Quadriceps (nM/kg LM legs)			
baseline	5.4 ± 0.9	6.0 ± 1.6	
post-training	6.3 ± 1.0	6.3 ± 1.4	$F_{(1,27)}$ =2.956; p=0.097
Body composition			
Body weight (kg)			
baseline	74.8 ± 16.5	74.4 ± 14.1	
post-training	74.7 ± 17.0	74.2 ± 14.1	$F_{(1,29)}$ =0.121; p=0.730
BMI (kg/m^2)			
baseline	25.5 ± 4.4	25.9 ± 3.5	
post-training	25.5 ± 4.7	25.8 ± 3.5	$F_{(1,29)}$ =0.198; p=0.660
LBM (kg)			
baseline	47.7 ± 9.5	48.2 ± 10.5	
post-training	47.2 ± 10.1	48.1 ± 11.0	$F_{(1,29)}$ =0.189; p=0.664
FM (kg)			
baseline	24.5 ± 12.1	23.6 ± 8.1	
post-training	24.9 ± 12.7	23.4 ± 8.2	$F_{(1,29)}$ =0.945; p=0.339
BF (% of BW)			
baseline	31.7 ± 10.4	31.6 ± 7.4	
post-training	32.2 ± 11.1	31.6 ± 7.7	$F_{(1,29)}$ =0.477; p=0.495

Data given as mean ± SD; [a] F-ratio=F-ratio of the effects of 'steroid group'; ST+=steroid-based immunosuppression; ST-=steroid-free immunosuppression; W=work load; VO_2=oxygen uptake; BW=body weight; LBM=lean body mass; RER=respiratory exchange ratio; LM=lean mass; BMI=body mass index; FM=fat mass; BF=body fat.

Discussion

The twelve-weeks lasting intensive, supervised exercise training program did have beneficial effects on exercise capacity, muscle function, and QoL in RTx and HD patients. Low maintenance doses of corticosteroids did not appear to compromise the response to training in RTx patients. Interestingly, the functional response to the standardized training program did not differ between RTx and HD patients, and healthy, sedentary controls. A remarkable difference was, however, found between renal patients and controls in body compositional changes.

Exercise capacity and muscle strength did significantly improve over the training period both in renal patients and controls. The improvements are in agreement with earlier published data on the effects of physical exercise in RTx patients[8-10]. Also in HD patients, beneficial effects on exercise capacity and muscle strength have been reported during both supervised exercise training on nondialysis days and training during hemodialysis sessions[1,11-15]. Training on nondialysis days appeared to be most effective[16]. However, comparing the results of studies towards the effects of exercise training remains difficult because of differences in composition, duration, and intensity of the training programs.

In contrast to the hypothesis of the study, improvement in exercise capacity and muscle strength in response to physical training was not significantly different between the RTx, HD, and control group. This finding underscores the importance of physical inactivity as a contributory factor to reduced exercise capacity and muscle strength in both RTx and HD patients. However, exercise capacity and muscle strength in RTx and HD patients after the training period generally remained lower than the baseline levels of controls. Indeed, exercise capacity and strength at baseline were significantly lower in RTx and HD patients than in controls, while - strikingly - no significant differences were observed between the patient groups[7]. Given the prolonged inactivity in the renal patients, the duration of the training program might have been too short to accomplish a further increase of exercise capacity and muscle strength. Moreover, it is quite possible that a higher anabolic stimulus (i.e., more specific resistance training) may be needed to further increase or normalize muscle strength in the patient groups. Skeletal muscle strength is found to be a highly significant predictor of exercise capacity in RTx and HD patients[7,24]. Therefore, a further increase of muscle strength is probably needed to optimize exercise capacity. More long-term interventions are needed to assess whether a normalization of exercise capacity and muscle strength can be achieved in renal patients.

Physical training did not have important effects on body composition in RTx and HD patients. LBM did, however, increase significantly in controls, particularly in males. Also Painter et al.[10] did not find changes in body composition of RTx patients after twelve months of cardiovascular exercise training. Macdonald et al.[25] did not observe changes in LBM of HD patients after three months of intensive cycle-training either. Horber et al.[26,27], however, reported a significant increase of thigh muscle mass in RTx patients after fifty days of specific resistance training. Moreover, Kouidi et al.[1] showed impressive effects of a twelve-weeks lasting training program (consisting of endurance and strength training) on muscular atrophy in HD patients. Finally, Castaneda et al.[28] found that twelve weeks of intensive resistance training counteracted the wasting associated with chronic uremia. In the present study, the training program consisted of endurance and strength training. The latter consisted of once a week specific resistance training and once a week strength-endurance training. Therefore, the anabolic stimulus necessary to counteract the catabolic effects associated with renal failure and necessary to accomplish an increase in muscle mass in renal patients might have been too mild. However, this does not explain the discrepancy between functional and anabolic changes which appeared to be present in renal patients but not in controls. Possibly, the exercise training might have induced intrinsic changes in the skeletal muscles, which did not result in an increase of the total LBM, but which may have contributed to the observed improvement of muscle strength and exercise capacity.

QoL improved in all scales scores in both the RTx and HD group, but most markedly in the scales related to physical functioning. Earlier studies in RTx and HD patients have shown exercise training to improve health-related QoL significantly too. Also these studies reported in particular the domains related to physical functioning to improve[10,15,29-31]. In RTx patients, no relationship between self-reported physical functioning and outcomes has yet been established. In HD patients, however, the PCS of the SF-36 is reported to be a consistent, powerful predictor of morbidity and mortality[32-34]. As expected, changes in QoL in controls were negligible, since the upper limits in most of the domains were already reached at baseline.

Glucocorticoids are known to cause muscle weakness and atrophy, which could result in a reduced exercise capacity[26,27,35]. Therefore, the use of steroids may be a limiting factor for exercise training in RTx patients. In the current study, we did not find any differences in baseline levels of exercise capacity, muscle strength, and LBM of RTx patients using low doses of steroids (5-10 mg/day) and patients on a steroid-free regimen[7]. Moreover, the response to training appeared to be not significantly different between these subgroups.

Exercise capacity and muscle strength equally increased, whereas in both groups no changes in LBM were observed. These results should, however, be interpreted with caution, because our study was not primarily designed to assess differences in response to training between subgroups of RTx patients.
Earlier studies of our group[36] and the group of Painter et al. [37] also showed no differences in body composition between RTx patients using and not using low dosages of steroids. In contrast to our study, Painter et al.[37] did observe significantly larger gains of VO_2peak and quadriceps strength in their steroid withdrawal group compared to their steroid group in the first year after transplantation. Comparison of the results of these studies is, however, difficult as Painter et al.[37] studied patients earlier after transplantation.
To the best of our knowledge, no other studies compared the response to training in RTx patients using or not using steroids. Horber et al.[26] reported that isokinetic resistance training increased muscle area and normalized muscle strength in RTx patients on low to moderate doses of steroids and that the increases in strength were comparable to those in healthy subjects undergoing similar training, which is in line with our results.

In the present study, only clinically stable RTx and HD patients without severe co-morbidity and able to perform maximal exercise testing were included. In particular patients suffering from cardiovascular disease and/or diabetes - both highly prevalent in the general RTx and HD population - were excluded. This limits the generalizability of the study. Selection bias is, however, found in most exercise studies in renal patients. Only in the Renal Exercise Demonstration Project[30,31], HD patients more representative of the general HD population in terms of co-morbidity and age, were included. Nearly 50% of the patients in that study did not complete the physical functioning tests[31]. Although exercise counseling improved physical functioning in these HD patients, there was a lesser magnitude of improvement.
Other limitations of our study are the unequal numbers of males and females in the HD group (this problem was, however, solved by correcting for gender in the statistical analyses) and the wide range in post-transplantation time (post-Tx time) and time since starting HD (post-HD time). Regarding the last, however, no relationships were observed between post-Tx time or post-HD time and baseline levels of exercise capacity, muscle strength, and body composition or the response to training with regard to these parameters.

The present study underscores the clinical importance of exercise training in RTx and HD patients. Exercise training therefore has to be considered as part of the routine treatment of both RTx and HD patients. Whether the beneficial effects of a short-term, intensive exercise program on physical performance and QoL persist after completion of the program and whether such a program

accomplishes an altered life-style towards regular physical activity still has to be established. More research is needed to unravel strategies to maintain improvement in physical performance and QoL in renal patients.

Conclusions

The twelve-weeks lasting, intensive, supervised exercise training program did have beneficial effects on exercise capacity and skeletal muscle strength in both RTx and HD patients. These effects coincided with a significant improvement of the self-reported health-related quality of life. The exercise training program did not have important effects on body composition in RTx and HD patients. The use of low maintenance doses of corticosteroids did not appear to compromise the response to training in RTx patients. Interestingly, the functional response (i.e., the response regarding exercise capacity and skeletal muscle strength) to the standardized exercise program did not differ in RTx patients, HD patients, and healthy, sedentary controls.

References

1. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Tourkantonis A, Deligiannis A. The effects of exercise training on muscle atrophy in haemodialysis patients. Nephrol Dial Transplant 1998; 13(3):685-99.
2. Painter P, Messer-Rehak D, Hanson P, Zimmerman SW, Glass NR. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron 1986; 42(1):47-51.
3. Kopple JD, Storer T, Casburi R. Impaired exercise capacity and exercise training in maintenance hemodialysis patients. J Ren Nutr 2005; 15(1):44-48.
4. Moore GE, Brinker KR, Stray-Gundersen J, Mitchell JH. Determinants of VO2peak in patients with end-stage renal disease: on and off dialysis. Med Sci Sports Exerc 1993; 25(1):18-23.
5. Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH. Uremic myopathy limits aerobic capacity in hemodialysis patients. Am J Kidney Dis 1993; 22(2): 277-287.
6. Painter P, Hanson P, Messer-Rehak D, Zimmerman SW, Glass NR. Exercise tolerance changes following renal transplantation. Am J Kidney Dis 1987; 10(6):452-456.
7. van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Franssen FM, Akkermans MA, Janssen PP, van Hooff JP. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. Am J Transplant 2005; 5(8):1957-1965.
8. Kempeneers G, Noakes TD, van Zyl-Smit R, Myburgh KH, Lambert M, Adams B, Wiggins T. Skeletal muscle limits the exercise tolerance of renal transplant recipients: effects of a graded exercise training program. Am J Kidney Dis 1990; 16(1):57-65.
9. Miller TD, Squires RW, Gau GT, Ilstrup DM, Frohnert PP, Sterioff S. Graded exercise testing and training after renal transplantation: a preliminary study. Mayo Clin Proc 1987; 62(9): 773-777.
10. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL. A randomized trial of exercise training after renal transplantation. Transplantation 2002; 74(1): 42-48.
11. Painter PL, Nelson-Worel JN, Hill MM, Thornbery DR, Shelp WR, Harrington AR, Weinstein AB. Effects of exercise training during hemodialysis. Nephron 1986; 43(2):87-92.
12. Koufaki P, Mercer TH, Naish PF. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. Clin Physiol Funct Imaging 2002; 22(2):115-124.
13. Headley S, Germain M, Mailloux P, Mulhern J, Ashworth B, Burris J, Brewer B, Nindl B, Coughlin M, Welles R, Jones M. Resistance training improves strength and functional measures in patients with end-stage renal disease. Am J Kidney Dis 2002; 40(2):355-364.
14. DePaul V, Moreland J, Eager T, Clase CM. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am J Kidney Dis 2002; 40(6):1219-1229.
15. Vilsteren van MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. Nephrol Dial Transplant 2005; 20(1):141-146.
16. Kouidi E, Grekas D, Deligiannis A, Tourkantonis A. Outcomes of long-term exercise training in dialysis patients: comparison of two training programs. Clin Nephrol 2004; 61 (Suppl 1): S31-38.
17. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry. J Am Soc Nephrol 1999; 10(5):1067-1079.
18. Rothkrantz-Kos S, Bekers O, Gubbels A, Drent M, Schmitz MP, van Dieijen-Visser MP. Evaluation of two new high-sensitivity methods for C-reactive protein. Ann Clin Biochem 2003; 40(Pt 4):398-405.
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16(1):31-41.
20. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982; 36(5):936-942.
21. Stewart AL, Ware JE. Measuring functioning and well-being: the medical outcomes study approach. Duke University Press, Durham, NC. 1992.

22. Ware JE. SF-36 health survey: manual and interpretation guide. Boston, MA: The Health Institute: New England Medical Center; 1993.
23. Ware JE, Kosinski M, Keller, SD. SF-36 physical and mental health summary scales: a user's manual. 2nd Edn. Boston, MA: The Health Institute: New England Medical Center; 1994.
24. Diesel W, Noakes TD, Swanepoel C, Lambert M. Isokinetic muscle strength predicts maximum exercise tolerance in renal patients on chronic hemodialysis. Am J Kidney Dis 1990; 16(2):109-114.
25. Macdonald JH, Marcora SM, Jibani M, Phanish MK, Holly J, Lemmey AB. Intradialytic exercise as anabolic therapy in haemodialysis patients - a pilot study. Clin Physiol Funct Imaging 2005; 25(2):113-118.
26. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Evidence that prednisone-induced myopathy is reversed by physical training. J Clin Endocrinol Metab 1985; 61(1):83-88.
27. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Thigh muscle mass and function in patients treated with glucocorticoids. Eur J Clin Invest 1985; 15(6):302-307.
28. Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, Fielding RA, Roubenoff R, Singh MF. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. Ann Intern Med 2001; 135(11):965-976.
29. Levendoglu F, Altintepe L, Okudan N, Ugurlu H, Gokbel H, Tonbul Z, Guney I, Turk S. A twelve week exercise program improves the psychological status, quality of life and work capacity in hemodialysis patients. J Nephrol 2004; 17(6):826-832.
30. Painter P, Carlson L, Carey S, Paul SM, Myll J. Low-functioning hemodialysis patients improve with exercise training. Am J Kidney Dis 2000; 36(3):600-608.
31. Painter P, Carlson L, Carey S, Paul SM, Myll J. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis 2000; 35(3):482-492.
32. DeOreo PB. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. Am J Kidney Dis 1997; 30(2):204-212.
33. Lowrie EG, Curtin RB, LePain N, Schatell D. Medical outcomes study short form-36: a consistent and powerful predictor of morbidity and mortality in dialysis patients. Am J Kidney Dis 2003; 41(6):1286-1292.
34. Knight EL, Ofsthun N, Teng M, Lazarus JM, Curhan GC. The association between mental health, physical function, and hemodialysis mortality. Kidney Int 2003; 63(5):1843-1851.
35. Perkoff GT, Silber R, Tyler FH, Cartwright GE, Wintrobe MM. Studies in disorders of muscle. XII. Myopathy due to the administration of therapeutic amounts of 17-hydroxycorticosteroids. Am J Med 1959; 26(6):891-898.
36. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation 2000; 69(8):1591-1598.
37. Painter PL, Topp KS, Krasnoff JB, Adey D, Strasner A, Tomlanovich S, Stock P. Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients. Kidney Int 2003; 63(6):2309-2316.

Chapter 9

General discussion
Summary
Conclusions

Introduction

Renal transplantation is undoubtedly the therapy of choice for end-stage renal disease (ESRD) patients, provided they are medically fit enough to undergo the transplant procedure. The probability of survival of renal transplant (RTx) patients is significantly superior compared to dialysis patients on the waiting list for transplantation[1,2]. Moreover, renal transplantation has important beneficial effects on quality of life (QoL)[2-4].

Most of the research in RTx patients has focused on the use of immune suppressive agents and prevention of acute and chronic rejection. However, other important issues - such as the influence of renal transplantation on nutritional status and physical performance - have not yet been widely investigated. Malnutrition and exercise intolerance are very common in dialysis patients[5-7]. It is generally assumed that the nutritional state and exercise capacity improve after renal transplantation[8-10]. However, little detailed information is present on alterations in body composition and exercise capacity and the determinants of these parameters in RTx patients. Potential determinants in the RTx patients are the reversal of the uremic state, the use of immunosuppressive agents (in particular corticosteroids), the often suboptimal renal function, and the lack of physical activity.

In this thesis, post-transplant changes in body weight and body composition, and the determinants of post-transplant changes in body weight and of body composition and exercise capacity, were investigated in RTx patients. Reliable, accurate methods are needed to be able to investigate (changes in) body composition in RTx patients. As there is no single full proof method of assessing body composition in this patient group, different techniques used to evaluate body composition were assessed and compared in RTx patients. In addition, the effects of exercise training on body composition and physical fitness were assessed and compared in RTx patients, hemodialysis (HD) patients, and healthy controls.

Effects of renal transplantation on body weight

Malnutrition is a common feature in HD patients. The actual body weight of a lot of HD patients is far below the ideal body weight, both as a result of loss of lean body mass (muscle wasting) and loss of body fat mass, probably due to a multifactorial process[5,6]. Factors which might be involved are a reduced appetite, chronic inflammation, metabolic acidosis, resistance to anabolic hormones, and catabolic effects induced by the dialysis procedure per se, such as bio-incompatibility and the loss of nutrients into the dialysate[11-13] (reviewed in chapter 1). A successful renal transplantation may improve or reverse the

factors associated with weight loss in dialysis patients. However, not all dialysis patients are necessarily malnourished and, apart from improvement in nutritional state, obesity may also arise in RTx patients.

Several studies indicate that pre-transplant mild (body mass index (BMI)>25 kg/m^2) or severe (BMI>30 kg/m^2) obesity are associated with significantly decreased patient and renal allograft survival[14-18]. RTx recipients are at risk for excessive weight gain after renal transplantation[19-26]. This post-transplant weight gain is associated with an increased risk of developing traditional risk factors for cardiovascular morbidity and mortality, such as hypertension, hyperlipidemia, insulin resistance, and post-transplant diabetes mellitus[27]. The development of obesity (BMI>30 kg/m^2) after renal transplantation is reported to significantly decrease five- and ten-year graft and patient survival rates[27]. Furthermore, the findings of a recent study by Micozkadioglu et al.[28] suggest that excessive weight gain after living-related renal transplantation may be an additional risk factor for the development of chronic allograft nephropathy.
Therefore, obesity may have far-reaching consequences in RTx patients. The increasing prevalence of overweight and obesity in ESRD patients undergoing renal transplantation is worrisome. Potential factors which may account for this increasing prevalence are 1) the increasing incidence of diabetes, an important risk factor of both chronic renal failure and obesity[29-32], 2) the fact that more patients at increased risk for obesity (e.g., older patients) are undergoing transplantation[30,33], 3) the better management of uremia during ESRD over recent years, which could theoretically improve dietary intake before transplantation[30], and 4) the behavioral and cultural influences that have encouraged excess caloric consumption and/or inadequate physical activity in the general population and that also may be manifest in patients with ESRD[34].

The changes in body weight after renal transplantation have not been widely investigated. In the study reported in chapter 2, post-transplant changes in body weight were assessed in a cohort of RTx patients[35]. Body weight decreased significantly in the first month after transplantation. After the first month, RTx patients started to gain weight. The mean weight gain in the first year after transplantation was 3.9 kg. After the first year, body weight gradually increased further; five years after transplantation, patients had gained on the average 6.2 kg (≈10%) in weight. In comparison, studies of other research groups showed weight gains of 5.5 to 14.2 kg in the first year after transplantation in patients who did not receive a specific dietary intervention[19-23,25]. The mean weight gain in the first five years after renal transplantation is reported to range between 10-20%[20,26]. The observed weight gain in our study was relatively low compared with post-transplant weight gains reported in the

literature. The fact that our patients were using relatively low maintenance doses of steroids (0 mg or 5 mg per day) might provide an explanation. Patients in the international studies mentioned, received high maintenance doses of corticosteroids (10 mg per day or more). Also in the study reported in chapter 4 in which post-transplant weight gain was studied in RTx patients on 10-mg steroid maintenance therapy, greater weight gains in the first six months after transplantation were observed (mean weight gain 4.0 kg) [36].

Weight gain is a known complication of corticosteroid maintenance therapy[37-39]. The effects of low maintenance doses of corticosteroids on body weight in RTx patients have, however, not been widely studied. Therefore, as reported in chapter 2, differences in post-transplant body weight course between a 5-mg maintenance corticosteroid regimen and a corticosteroid withdrawal regimen were compared[35]. The RTx patients on the withdrawal regimen were free of steroids at a mean of 7.3±2.6 months after transplantation. They were then maintained on cyclosporine mono-therapy. The group of patients undergoing 5-mg steroid maintenance therapy was divided into patients who experienced rejection treated with steroid boluses and therefore increasing the cumulative steroid dose, and patients who did not experience rejection. In the first year post-transplantation, weight gain was not significantly different in the steroid withdrawal and steroid maintenance group, irrespective of the need for rejection therapy; moreover, no relationship was observed between the weight gain in this period and the cumulative dose of steroids. However, in the longer-term post-transplant period cumulative steroid dose appeared to have a significant effect on body weight increase: the higher the cumulative steroid dose, the greater the weight gain.
These results are in agreement with the results of Johnson et al.[26], who did not find a significant relationship between weight gain and the cumulative steroid dose in the first year after transplantation either, even while the cumulative steroid dose in the Johnson study was substantially higher than the steroid dosage in our study. In contrast, a recent study by Rogers et al.[23] reported weight gain in the first year after renal transplantation to be significantly smaller in RTx patients with early corticosteroid withdrawal (i.e., within seven days post-transplantation) compared to patients on chronic steroid therapy. They did, however, not mention the (cumulative) steroid dose in the chronic steroid group. Moreover, Ratcliffe et al.[40] found, in a randomized controlled trial, that RTx patients allocated to a ‘late’ steroid withdrawal group (i.e., start withdrawal at a mean of two years post-transplantation) had a slight but significant reduction in body weight, whereas over the same follow-up period there was a slight increase of body weight in the control group, which was maintained on a steroid dose of about 10 mg per day. Evidently, these results are conflicting,

and more randomized trials are needed to assess definitively the influence of low-dose steroids on post-transplant weight gain.

In the study reported in chapter 2, pre-transplant BMI was found to be a significant predictor of post-transplant weight gain[35]. RTx patients with a pre-transplant BMI>25 kg/m^2 had significantly lower weight gains compared to patients with a BMI between 20 and 25 kg/m^2; this latter group in its turn had significantly lower weight gains compared to patients with a pre-transplant BMI<20 kg/m^2. Pre-transplant BMI appeared to be related to pre-transplant dialysis modality: HD patients had significantly lower body mass indices compared to continuous ambulatory peritoneal dialysis (CAPD) patients. The greater weight gain in the RTx patients with a low BMI - the majority on HD therapy before transplantation - might indicate an improvement in their nutritional state. Many HD patients are suffering from malnutrition, usually characterized by both fat and lean body mass depletion. In such cases, post-transplant weight gain is not necessarily a negative finding.
The above mentioned findings regarding pre-transplant BMI differ from the results presented in other studies. On the one hand pre-transplant obese RTx patients are reported to gain significantly more weight after transplantation compared to non-obese patients[21,24,25]. On the other hand Johnson et al.[26] reported no significant differences in post-transplant weight gain between pre-transplant obese and non-obese RTx patients.

There are some important issues biasing the assessment of weight changes in the RTx population. Firstly, the so-called dry weight of the RTx patients before transplantation may not have been assessed adequately. Dry weight is the weight at the end of dialysis at which moment hydration state is supposed to be normal. It is notoriously difficult to adequately estimate dry weight by clinical measurements. More sophisticated methods to assess dry weight, such as measurement of the inferior vena cava diameter, are not implemented in the everyday clinical practice. Secondly, after transplantation rapid changes in hydration state may occur as a result of a decreased kidney function or impaired cardiac function and the use of medication such as steroids or antihypertensive agents, which may affect the changes in post-transplant body weight.
Thus, more important than the post-transplant weight gain itself is the nature of the excess weight. A major point of concern is raised when the post-transplant increase in body weight is primarily due to an increase of body fat mass. Too large an increase in body fat mass - in particular in visceral fat mass - could have adverse effects on the lipid metabolism, insulin resistance and atherogenesis in RTx patients, which is likely to be of importance in view of the high cardiovascular morbidity and mortality in these patients[41-43].

In summary, body weight significantly increases after renal transplantation. Apart from a potential improvement of the nutritional state, excessive weight gain can lead to the development of obesity. Obesity is strongly associated with an increased risk of cardiovascular morbidity and mortality. Moreover, obesity is associated with a significantly decreased graft and patient survival. Changes in body weight are, however, an unreliable indicator of changes in body composition. To investigate (changes in) body composition in RTx patients, reliable, accurate methods are needed. Therefore, in chapter 3 different techniques used to assess body composition were compared in RTx patients.

Methods to assess body composition in renal transplant patients

Multi-frequency bio-electrical impedance analysis (MF-BIA) and anthropometry - assuming the body as a two-compartment model, consisting of fat mass (FM) and fat-free mass (FFM) - are easily applicable and relatively cheap methods to assess body composition. Dual energy x-ray absorptiometry (DEXA) assumes the body as a three-compartment model and measures total and regional body FM, lean body mass (LBM; comprising muscle, inner organs and total body water) and bone mineral content[44,45]. DEXA cannot determine visceral fat, but it can measure central abdominal fat. Central abdominal fat includes the visceral fat in this region plus anterior and posterior subcutaneous fat. Published studies have shown a good correlation between central abdominal fat by DEXA and visceral fat by CT or MRI[46-48].

DEXA measures body composition with high precision[44,45,49,50], but is more complicated to perform and more expensive compared to MF-BIA and anthropometry. Moreover, patients are exposed to (low doses of) radiation. Although DEXA is not a gold standard, it has been widely applied for studies of body composition in dialysis and RTx patients[51-53] and it has been proposed by the Kidney Disease Outcomes Quality Initiative (K-DOQI) as a reference method to assess body composition in renal patients[54].

The estimate of body FM by DEXA is not affected by hydration state[55-59]. Hydration state does, however, affect the estimate of LBM[45,50]. DEXA cannot properly distinguish between extra-cellular and intracellular water (ECW and ICW) volume and includes excess ECW in the LBM[50]. Therefore, in patients with disturbances in fluid status, such as patients with end-stage renal failure, LBM assessed by DEXA should be corrected for the ECW volume.

In chapter 3, it was investigated whether MF-BIA or anthropometry could replace DEXA in the analysis of body composition in RTx patients. For this, MF-BIA, anthropometry, and DEXA were compared to one another for measurement of the body fat and fat-free compartment in a cohort of 77 RTx

patients who were at least two years after renal transplantation and who had a stable renal function. Furthermore, MF-BIA was compared to isotope dilution techniques (which are considered the gold standard for measuring body water compartments in healthy individuals) for measurement of body water compartments[60].

With regard to the assessment of body fat, expressed as percentage of body weight, method agreement between DEXA and anthropometry and between DEXA and MF-BIA appeared to be acceptable (original intraclass correlation coefficient (ICC) 0.913 and 0.887, respectively)[60]. The limits of agreement between DEXA on the one hand and anthropometry and MF-BIA on the other hand were, however, relatively wide. Moreover, the ICC values in specific subcategories of RTx patients did not meet the acceptable level of method agreement between DEXA and anthropometry and between DEXA and MF-BIA. This indicates a questionable reliability of anthropometry and MF-BIA in the assessment of FM and FFM in RTx patients. On the basis of these findings, DEXA was used to assess body composition in RTx patients in the present thesis.

With regard to the assessment of the body water compartments in RTx patients, method agreement between MF-BIA and deuterium isotope dilution for measuring the amount of total body water (TBW) was found to be good (original ICC and ICC values of the various subgroups of RTx patients all >0.886)[60]. Therefore, for measuring TBW in RTx patients, the deuterium isotope dilution technique might be substituted by MF-BIA. In contrast, method agreement between bromide isotope dilution and MF-BIA for measurement of the ECW volume was less satisfactory (original ICC and ICC in most of the subcategories of RTx patients <0.85). However, possible limitations of the bromide isotope dilution technique have to be taken into account[61]. More research is needed to investigate the validity of MF-BIA for measurement of ECW in RTx patients.

The reliability of MF-BIA with regard to the assessment of the absolute magnitude of the ECW volume appears to be reduced in overhydrated (dialysis) patients[62]. Nevertheless, MF-BIA adequately predicts relative changes in ECW volume[62]. In this thesis, there was particular focus on the relative changes of ECW in dialysis patients and not so much on the assessment of the absolute magnitude of ECW. Therefore, MF-BIA was - also due to the difficulty in the practical implementation as well as the costs of tracer dilution methodology - used to get insight in the changes of the extra-cellular volume in RTx and dialysis patients.

In summary, in the present thesis DEXA was used to assess body composition in renal patients. DEXA includes excess ECW in the LBM. For practical reasons, ECW was measured by MF-BIA.

Effects of renal transplantation on body composition

In the prospective study reported in chapter 4, changes in body composition in the first six months after renal transplantation were assessed in a group of 11 RTx patients without severe intercurrent disease or episodes of acute rejection[36]. Patients were treated with prednisolone (10 mg maintenance dose), tacrolimus and mycophenolate mofetil (MMF). Post-transplant weight gain appeared to be predominantly due to an increase in FM. Mean body FM, assessed by DEXA, significantly increased by 3.2 kg, whereas only a slight, non-significant increase (0.8 kg) in LBM was observed. The increase in body fat was most pronounced in the truncal region.
The results concerning the increase in FM are in agreement with the results of other studies which addressed the impact of renal transplantation on body composition in the first six months after transplantation[63-65]. Painter et al.[66,67] studied changes in body composition in the first year after kidney transplantation. They too found the (significant) weight gain in this period to be primarily due to an increase in FM. Steiger et al.[68] reported total FM to significantly increase over the first 16 months after transplantation, whereas the increase in LBM was much less pronounced; initially, LBM appeared to decrease between day 11 and 42 after transplantation. This was probably due to a reduction in the degree of overhydration of the patients rather than to a decrease of muscle mass. Also in an earlier cross-sectional study of our research group (chapter 6) - 77 RTx patients with a mean follow-up time of 9.1 years after transplantation were studied - the percentage of total body fat was found to be very high, especially in female patients[69]. The percentage of body fat averaged 24.0% in males and 37.9% in females, whereas the ideal percentage of body fat for subjects aged 30 years or more is 15-20% in males and 20-25% in females[70].

Summarizing, body weight was found to significantly increase after renal transplantation. The post-transplant weight gain appears to be primarily due to an increase in body FM. This might have untoward effects on the cardiovascular risk profile of RTx patients. Potential factors involved in the increase in body FM after renal transplantation are 1) the use of immunosuppressive agents, in particular corticosteroids, 2) post-transplant changes in dietary intake, and 3) the lack of physical activity. These factors will be discussed below.

The influence of corticosteroids on body composition in RTx patients

Glucocorticoids have important effects on body composition. The long-term use of steroids can cause weight gain, centripetal obesity and skeletal muscle wasting (see general introduction). It remains unclear whether the changes in body composition after renal transplantation (i.e., the increase of the body FM) are due to the steroid immunosuppressive therapy.

In a cross-sectional study in 77 RTx patients who were on average 9.1 years after renal transplantation at the time of body composition measurements (chapter 6), no differences were found in body FM, LBM or body fat distribution in the patients with a maintenance steroid dose of respectively 0 mg, 5 mg or 10 mg per day[69]. Patients in the 0-mg group had discontinued steroids for a mean period of 7.0 years. A significant relationship between the body composition parameters and the cumulative steroid dose was not observed either. Although body composition was not measured in a group of age- and sex-matched healthy controls, the mean percentage of body fat in this group of RTx patients was - as discussed earlier - relatively high. Moreover, the waist-to-hip ratio (a measure of trunk fatness / proportion of fat in the trunk) was so high in 12% of the male patients and 66% of the female patients (i.e., above 1.00 in the males and above 0.80 in females), that their risk of metabolic abnormalities, hypertension, diabetes mellitus and cardiovascular disease was significantly increased[71,72]. Preferential abdominal accumulation of body fat -also observed in the prospective study[36] reported in chapter 3- is one of the well-known side-effects of high-dose glucocorticosteroid treatment. Abdominal fat cells have a high glucocorticosteroid receptor density. In addition, the activity of the lipoprotein lipase - the main regulatory enzyme of lipid uptake by abdominal adipocytes - is dependent on circulatory levels of endogenous and exogenous glucocorticosteroids[73,74]. Moreover, lipolytic activity in fat cells in the abdominal region has been found to be low in patients with Cushing's disease (i.e., in patients with chronic corticosteroid excess)[73]. Together, these findings contribute to the often observed 'altered' body fat distribution in patients on steroid therapy, which is characterized by increased central fat stores in the presence of normal, or even increased, peripheral fat stores.

Mathieu et al.[75] measured body composition in 18 RTx patients (mean time since transplantation 64 months) on immunosuppressive mono-therapy with cyclosporine A. Body composition data of the RTx patients in that study, who were free of steroids for a median of more than three years, were compared to those of healthy, age-, sex- and BMI-matched controls. The results of the study demonstrated that a decreased LBM (particularly due to a decreased lean

mass in arms and legs), an increased body FM, upper-body obesity and moon-face, characteristics which are usually present in patients on high-dose glucocorticoid therapy[37,38,76-79], persist for years after discontinuation of steroid therapy. FM of head and neck tended to increase with a longer application of steroid therapy and increasing cumulative steroid dose, whereas the decreased LBM and increased truncal FM were not related to the cumulative steroid dose, months on steroid therapy, mean daily steroid dose, or time off steroids. The results of our cross-sectional study[69] and of the study of Mathieu et al.[75] suggest that the effects of discontinuation of steroid therapy in the later post-transplant period on body composition in RTx patients are relatively small.

In the study reported in chapter 5, in which patients were randomized to either steroid therapy (10 mg/day) or steroid withdrawal three months after renal transplantation, the increase in FM three months later (assessed by DEXA), tended to be higher in the RTx patients randomized to continue steroids[80]. Drawbacks of this study are the rather small number of patients studied and the short follow-up period. It is, however, likely that the effects of steroids on body composition are most pronounced in the early post-transplant period, when steroid doses are relatively high. Moreover, in the longitudinal study reported in chapter 2, a significant, positive relationship was observed between the cumulative steroid dose and body weight gain after the first post-transplantation year[35].
In a prospective study, Steiger et al.[68] also observed significant increases in body FM over the first 16 months after renal transplantation in patients who received significant amounts of steroids (mean cumulative dose of steroids over this period was approximately 8 g) and who were advised to restrict their dietary energy intake, whereas the body fat distribution did not change over the observation period. Furthermore, the mean daily steroid doses were found to be inversely related to lipid oxidation, suggesting that corticosteroids might affect body composition in a dose-dependent manner. Moreover, also in the prospective study by Painter et al.[67] in which lower doses of steroids were used (maintenance doses ranging from 5-10 mg per day), significant increases in body FM over the first post-transplantation year were observed, whereas the increase in LBM was much less pronounced. More recently, the group of Painter et al.[66] compared changes in body composition over the first year following renal transplantation in patients with rapid elimination of steroids (within five days after transplantation) with patients managed with a immunosuppressive regimen that included steroids (maintenance dose ranging from 5-10 mg per day, reached within three months after transplantation). Body weight significantly increased in both patient groups. This was primarily due to a significant increase of body FM. LBM did not significantly change over the follow-up period. The post-transplant changes in body weight and body

composition were, however, not different between the RTx patients with and without steroids. In agreement, in the study reported in chapter 2, weight gain in the first year after transplantation appeared to be not related to the cumulative steroid dose[35].

There are some critical notes regarding the studies on the effects of steroids on body composition. Firstly, the effects of long-term use of high doses of corticosteroids on body composition in RTx patients have not been scrutinized in a prospective way. Secondly, from a historical point of view, the pharmaco-therapeutic developments in the last decades resulted in a broad range of immunosuppressive regimens in RTx patients with ever decreasing steroid doses. In the pre-cyclosporine era, high doses of corticosteroids were used in combination with azathioprine. After the introduction of cyclosporine, reductions in steroid doses could be achieved. Nowadays, new, potent immuno-suppressive agents such as tacrolimus (FK506), mycophenolate mofetil (MMF) and sirolimus, are commonly used in combination with low maintenance steroid doses. In our transplant center in Maastricht and in some other innovative transplant centers, even new immunosuppressive regimens are used in which steroids are being avoided or withdrawn in the early transplant period (i.e., in the first weeks following renal transplantation). Inherent to these recent pharmacological developments, immunosuppressive regimens - in particular steroid doses - in studies towards body composition of RTx patients vary considerably. Thirdly, specific data on cumulative steroid doses are lacking in most of the studies reported in the literature. Finally, in order to assess the effects of (different doses of) steroids on body composition, steroid doses should - from a scientific point of view - be related to the body weight of the patients. Unfortunately, an extensive literature search has shown that these data are only reported in a few studies. Exact information regarding both the cumulative and daily steroid doses (the latter expressed per kilogram body weight) is lacking in most of the studies and so comparison of studies towards the effects of steroids on body composition in RTx patients is difficult.

In summary, controversy remains whether and to which degree the changes in body weight and body composition after renal transplantation are due to steroid immunosuppressive therapy. More long-term, prospective, randomized studies are needed to answer this question.

Dietary intake and body composition

The dietary intake after a successful renal transplantation is generally expected to increase as a result of the increased feeling of well-being, the lack of dietary restrictions and the increased appetite of RTx recipients. A chronic increase of energy intake without an increase of the energy expenditure will inevitably increase the body weight. In the cross-sectional study reported in chapter 6, the daily energy intake of RTx patients was found to be only slightly lower than the mean energy intake in age-matched, healthy Dutch adults[36]. The nutrient intake of the RTx patients was in compliance with the Dutch Dietary Reference Intakes[81], in which a macronutrient composition of 30-35 energy percent of fat, 10-15 energy percent of proteins and 50-55 energy percent of carbohydrates is recommended. Therefore, the dietary intake of the RTx patients was indeed more adequate compared to the dietary intake in dialysis patients, in which the intake of energy and protein is reported to be insufficient in the vast majority of patients as compared with the recommended energy and protein requirements[82,83].

El Haggan et al.[84] found weight gain and the increase in body FM over the first year post-transplantation to be significantly associated with an increase in total energy intake. Moreover, Steiger et al.[68] reported dietary energy restriction in RTx patients receiving relatively high doses steroids to prevent the usually observed post-transplant fat accumulation in the trunk. In the cross-sectional study reported in chapter 6, however, no relationship was observed between the mean daily nutrient intake (measured by means of a three-day food record) and body composition or body fat distribution in RTx patients[69].

Patel et al.[19] found that intensive dietary counseling in the early post-transplant period was effective in controlling weight gain in the first year after renal transplantation in patients on triple immunosuppressive therapy (prednisolone, cyclosporine and azathioprine). The mean increase in body weight in the first year after transplantation was 5.5 kg in the patients who received intensive dietary counseling compared to 11.8 kg in patients who did not receive any dietary advice. The study did, however, not report body composition data. Lopes et al.[85] studied the effects of a dietary intervention (American Heart Association Step One Diet with a moderate caloric restriction) on body weight and body composition in RTx patients who had already an averaged 39 months post-transplantation status. All patients received steroids (mean dose 4.3±3.3 mg per day), cyclosporin, and azathioprine. The dietary measures resulted in a significant loss of body weight and body FM.

Concluding, careful dietary management aimed to balance caloric intake to energy expenditure, appears to have beneficial effects on body weight and body composition in RTx patients. Intensive dietary counseling should be given already in the early post-transplant period, with follow-up counseling on a regular basis.

Physical activity and body composition

Physical activity plays an important role in the prevention and treatment of obesity[86,87]. Moreover, regular physical activity is necessary for maintaining muscle mass and function[86]. Furthermore, low physical activity levels are associated with an increased mortality in the general population, and in particular with an increased cardiovascular mortality[86,88-90]. In healthy subjects, exercise training or simply increasing daily physical activity level results in an increase of LBM and - in general - in a decrease of body FM[87,91-97]. In addition, exercise appears to have favorable effects on body fat distribution[96-100].

Although no relationship was observed between steroid dose and body composition or between dietary intake and body composition in the study reported in chapter 6, physical activity level was significantly related to body composition in RTx patients[69]. It was inversely related to FM, and it was positively related to the percentage of LBM. The beneficial effects of physical activity on body composition appeared to be more pronounced in female RTx patients than in male RTx patients. Painter et al.[101] also found the percentage of body fat in physically active transplant games participants to be significantly lower than in physically inactive participants. In addition, they observed a trend towards a lower percentage of fat in active RTx patients when compared to inactive RTx patients[66,67].

Physical activity levels in patients receiving hemodialysis are extremely low compared to those of healthy sedentary controls[102,103]. Many patients remain physically inactive after successful renal transplantation[20,104], as also shown in the cross-sectional study[69] in chapter 6. Physical inactivity is an important risk factor for the development of the metabolic syndrome. This syndrome is characterized by a cluster of associated metabolic risk factors including atherogenic dyslipidemia, hypertension, hyperinsulinemia, glucose intolerance, prothrombotic and proinflammatory states, and abdominal obesity[105-108]. Patients suffering from the metabolic syndrome are at increased risk of coronary heart disease, peripheral vascular disease, stroke, and type 2 diabetes mellitus[109,110]. Moreover, metabolic syndrome is associated with impaired renal allograft function in RTx patients[111,112]. Metabolic syndrome is

highly prevalent both in non-diabetic ESRD patients and in RTx patients without a history of pre-transplant diabetes mellitus[112,115]. In RTx patients, the chronic use of immunosuppressive agents such as steroids, calcineurin inhibitors (especially cyclosporine) and mTOR inhibitors, is an additional contributing factor in the pathogenesis of the metabolic syndrome[116].

In healthy subjects, physical activity levels are significantly and positively related to exercise capacity and muscle strength, both important determinants of physical functioning and performance[117,118]. Exercise intolerance is common in HD patients[7,119-125] (many patients are even severely limited in their activities of daily life) and has a profound, negative impact on QoL. Exercise capacity appears to improve spontaneously after renal transplantation, but it often remains subnormal[9,10]. The reduced exercise capacity in RTx patients was hypothesized to be associated with physical inactivity.

In summary, physical activity was found to be related to body composition in RTx patients. The physical activity levels of RTx patients were reported to be low. Physical inactivity was hypothesized to be associated with exercise intolerance in RTx patients. It was however, not known to what extent exercise capacity and skeletal muscle strength of RTx patients differ from HD patients and age-matched, untrained, healthy subjects. Moreover, the potential determinants of exercise capacity in RTx patients had not been elucidated. Therefore, these aspects were studied in chapter 7 of this thesis.

Similarities in exercise capacity and skeletal muscle strength between RTx and HD patients

In the study described in chapter 7, it was assessed to what extent exercise capacity and skeletal muscle strength of RTx patients differ from HD patients and age-matched, untrained, healthy subjects. Mean peak oxygen uptake (VO_2peak) levels in RTx patients (21.3±6.2 ml/min/kg) - important indicators of exercise capacity - were comparable to those in HD patients (21.4±8.0 ml/min/kg), but significantly lower compared to the levels in healthy, age-matched, untrained controls (26.4±7.8 ml/min/kg). Skeletal muscle strength of the RTx patients was not different from that in HD patients either; it was however again significantly lower compared to controls. The observed VO_2peak levels in HD patients are in line with previous reported VO_2peak levels, which were in the range of approximately 15-22 ml/min/kg[126-130]. The VO_2peak levels in RTx patients were lower compared to levels reported in literature, ranging from 24-32 ml/min/kg[9,66,67,123,131]. It has, however, to be mentioned that comparison of VO_2peak levels is difficult, as the various studies

differ in characteristics of the study populations (i.e., age, co-morbid conditions et cetera) and in test-modalities for VO_2peak. Regarding the latter, VO_2peak levels measured by cycle-ergometry, as used in the present thesis, are reported to be 5-10% lower on average than for treadmill exercise performed by the same subjects[132].
Nearly 50% of the RTx patients had VO_2peak levels <20 ml/min/kg body weight, levels which are reported to be associated with severe functional limitations[133]. Thus, the exercise capacity in the RTx patients appears to be so low that many patients are even suffering from functional limitations in their activities of daily life. As a consequence, many patients are leading a sedentary life-style, which increases the risk of cardiovascular complications and which impairs their quality of life. Alternatively, physical inactivity may result in muscle wasting and muscle weakness, and may contribute to a reduced exercise tolerance. Exercise training programs or counseling to increase physical activity levels might interrupt this vicious circle.

In chapter 7, also the relationship between exercise capacity and its potential determinants was investigated in RTx patients[134]. Skeletal muscle strength and physical activity level appeared to be significant predictors of exercise capacity (indicated by VO_2peak) (see figure 7.1). In turn, muscle strength appeared to be significantly and positively related to LBM. Furthermore, renal function turned out to be a significant predictor of LBM, and through LBM, of muscle strength and exercise capacity, while no effects of the use of corticosteroids and of hemoglobin (Hb) levels were observed. Effects of Hb levels on exercise capacity were not expected, because Hb levels in the RTx patients (mean 8.6±1.0 mmol/liter) were comparable to the levels in the healthy controls (mean 8.9±0.8 mmol/liter). Moreover, the observed Hb levels in our group of RTx patients were significantly higher than 6.3 mmol/liter. Hb levels are reported to significantly affect exercise capacity when they drop below the limit of 6.3 mmol/liter[135,136].
Painter et al.[101] also observed a relationship between physical activity level and exercise capacity in RTx patients participating in the U.S. Transplant Games. They found physically active patients to have a significant higher VO_2peak (mean 34.6 ml/kg/min) than inactive patients (mean 23.6 ml/kg/min). In addition, the relation between physical activity level and VO_2peak has been established in healthy subjects[117]. Moreover, muscle dysfunction also has been found to be an important contributor of exercise intolerance in RTx patients, HD patients, and patients with chronic diseases such as COPD and congestive heart failure[126, 128,137-139].
The results of our study also suggest that, albeit through indirect effects, a subnormal renal function might play a role in the impaired exercise capacity of RTx patients. The mechanisms remain to be elucidated. Potential factors that

might be involved are for example a reduced protein intake, metabolic acidosis, systemic inflammation, and resistance to anabolic hormones.

In summary, we found exercise capacity and skeletal muscle strength in RTx patients to be significantly lower compared to healthy, sedentary controls, but not significantly different compared to HD patients. Regular physical activity appears to be an important determinant of exercise capacity in RTx patients. Exercise training has the potential to increase physical activity levels and, as a consequence, to improve exercise capacity in RTx patients. Therefore, in the study described in chapter 8, the effects of exercise training on body composition, exercise capacity, skeletal muscle strength, and QoL were assessed in RTx patients. These effects were compared with the effects of training in HD patients and healthy, untrained controls.

Effects of exercise training

Effects on body weight and body composition

In the study reported in chapter 8, the effects of exercise training (twice weekly during a period of twelve weeks) on body composition were investigated in RTx patients, HD patients, and healthy, untrained controls. The standardized exercise program consisted of a combination of endurance and strength training. Exercise training did not have important effects on body weight and body composition, assessed by DEXA, in RTx and HD patients. In contrast, body weight did increase significantly in controls, in particular in males, due to a significant increase of the LBM.
Only a few other studies towards the effects of exercise training on body composition were performed in RTx or HD patients. Painter et al.[67] found no effects of (cardiovascular) exercise training on body FM or LBM in RTx patients. In this study, as well as in our study, patients did not receive any dietary intervention. With regard to body FM, in healthy subjects exercise in combination with diet is shown to provide greater losses in body weight and body FM compared to either exercise or diet alone[140]. It is becoming increasingly clear from the scientific literature that exercise training, or simply a physically active life-style makes its major contribution by *preventing* weight gain, but not by inducing weight loss of those individuals who already have an established pattern of energy intake and expenditure that leads to an overweight or obese state. Thus, as also found in our study, exercise training alone does not appear to be sufficient to evoke changes in body FM in the RTx population. The use of corticosteroids appears not to affect the response to exercise training with regard to both body FM and LBM, as no differences were

observed in this response between RTx patients using low doses of steroids and patients on steroid-free immunosuppression (chapter 8).
Macdonald et al. [141] did not find changes in LBM in HD patients after intensive cycle-training either. However, other studies in which the exercise training program mainly consisted of specific resistance training did report training to increase LBM in HD patients[77,78,142,143]. This suggests that the anabolic stimulus necessary to counteract the catabolic effects associated with renal failure and necessary to accomplish an increase in muscle mass in renal patients might have been to mild in our study. Moreover, the absolute stimulus in the renal patients - which was lower in the patient groups than in the healthy controls, due to the standardized training program which was based on the results of the cycle and strength tests at baseline - might have been too low. Furthermore, the precision of DEXA might have been inadequate to detect small changes in body composition. Finally, a stronger anabolic stimulus might be necessary to counteract the resistance to anabolic hormones - such as growth hormone and insulin-like growth factor-I - which is associated with uremia. More research is needed to study the effects of exercise training on muscle mass in RTx and HD patients (particularly focused on different exercise modalities) and to get insight in (changes in) the skeletal muscle morphology and metabolism in these patient groups.

In summary, exercise training twice weekly during a period of twelve weeks appears not to be effective in the management of body weight and body FM in RTx patients. The use of corticosteroids appears not to affect the response to training with regard to body FM or LBM in RTx patients. Increased levels of daily physical activity are reported to be especially important in the *prevention* of weight gain. It is therefore of the utmost importance to focus on exercise programs and increasing physical activity levels in the earliest possible stages of chronic renal failure, i.e., in the pre-dialysis and dialysis period. Achieving a more active life-style may lower the risk for overweight and obesity after renal transplantation. In the post-transplant period, a combination of exercise and a dietary intervention is probably the most effective way for weight management. Future studies are necessary to unravel the best strategy for post-transplant weight management.

Effects on exercise capacity, skeletal muscle strength, and QoL

In chapter 8, the effects of a twelve-weeks lasting standardized exercise training program on exercise capacity, skeletal muscle strength, and QoL were investigated in RTx patients, HD patients, and healthy controls. Exercise capacity and muscle strength improved significantly and to the same extent in RTx and HD patients. The improvements coincided with significant

improvements in the self-reported QoL. Earlier studies also described beneficial effects of exercise training on exercise capacity and muscle strength in RTx and HD patients[9,67,124,142,144-148]. Comparing the results of studies on the effects of training is, however, difficult because of differences in composition, duration, and intensity of the training programs.

Interestingly, the functional response (i.e., the response regarding exercise capacity and muscle strength) to the exercise program did not differ between the RTx and HD patients, and healthy controls. This finding suggests that the use of corticosteroids and the (often subnormal) renal function in RTx patients do not affect the response to exercise training in this patient group. The fact that the response to exercise training appeared not to be significantly different between the RTx patients using steroids and the RTx patients on a steroid-free regimen, supports this suggestion. Moreover, the results suggest that the potential adverse effects of uremia, malnutrition, chronic inflammation, and the resistance to anabolic hormones on exercise capacity and muscle strength in HD patients can be counteracted by exercise training. It should however be noticed that we included only stable HD patients, on the waiting list for renal transplantation, without severe co-morbidity. Physical inactivity thus turns out to be an important contributing factor to the reduced exercise capacity and skeletal muscle strength in both RTx and HD patients.

Exercise capacity and muscle strength in the RTx and HD patients did not reach the baseline levels of healthy controls after completion of the training program, possibly because the training period was too short to accomplish a further increase of exercise capacity or muscle strength. In addition, a higher anabolic stimulus (i.e., more specific resistance training) may be needed to further increase skeletal muscle strength in RTx and HD patients. As skeletal muscle strength is found to be a highly significant predictor of exercise capacity in RTx and HD patients[126,134], a further increase of muscle strength is needed to optimize exercise capacity. Data of the study of Painter et al.[101] towards the health-related fitness of organ transplant recipients who participated in the U.S. Transplant Games suggest that near-normal or even higher levels of cardio-respiratory fitness and QoL can be achieved in transplant patients performing regular physical activity. Long-term interventions are needed to assess whether the same levels of exercise capacity and muscle strength as in age- and sex-matched healthy controls can be achieved in the general RTx and in the HD population. Moreover, more research is needed to elucidate the most effective training strategy in RTx and HD patients.

Exercise capacity is known to be an independent predictor of survival in healthy subjects and in several chronic diseases like heart failure, cystic fibrosis and

chronic obstructive pulmonary disease[149-154]. Recently, Sietsema et al.[155] reported that VO_2peak was a stronger predictor of survival than many traditional prognostic variables (i.e., nutritional, inflammatory and cardiovascular status, and co-morbidity) among relatively healthy HD patients. Although this finding is probably not true in the general HD population, exercise training at least has the potential to improve QoL in dialysis patients, since exercise training has shown to be able to increase VO_2peak levels[124,142,145].
Data about the prognostic value of exercise capacity in RTx patients are lacking. However, higher physical activity and exercise capacity levels may be expected to indirectly affect the survival rates in RTx patients, as they have the potential to reduce cardiovascular risk factors such as hypertension, hyperlipidemia, post-transplant diabetes mellitus and obesity, and therefore cardiovascular mortality in the RTx population. Indeed, Painter et al.[156] did observe the risk of coronary heart disease (CHD, measured by the Framingham CHD prediction method) to be significantly and negatively correlated to the maximal exercise capacity in a cohort of RTx patients. Cardiovascular disease is the leading cause of death following renal transplantation and, as a consequence of death with a functioning graft, it is a major cause of graft loss[157,158].

Health-related QoL assessments give insight into subjects' physical, psychological and social functioning. These domains of health are known to be strongly related to patients overall QoL[159,160]. The Medical Outcomes Study Short-Form-36 questionnaire (SF-36) is shown to be reliable and valid for measuring health-related QoL in both HD and RTx patients[161-164]. HD patients perceive a poor QoL. Self-reported physical functioning is severely limited and reported to be significantly lower than age-predicted norms[65,119,159,165-170]. In addition, general health, social functioning, and bodily pain are parameters which are found to be significantly affected[3,4]. Our data regarding QoL in the HD patients studied in chapter 8 are in agreement with the findings reported in the literature. QoL has been shown to improve after renal transplantation[3,4,171,172]. However, the majority of RTx patients perceives their health status as being substantially lower than that of the general population[3,173-175]. In chapter 8, no significant differences were observed in the SF-36 scale scores (except the vitality and role functioning score which were significantly lower in HD patients) and in the overall physical and mental composite scales between the HD and RTx patients. This might be due to the fact that the exercise capacity and skeletal muscle strength in the RTx patients were low and not significantly different compared to HD patients. However, the variation in the scale scores of the SF-36 makes that large sample sizes are necessary to determine significant differences between groups. As our study was not primarily designed to assess baseline differences in QoL between RTx and HD

patients, the number of patients studied might have been too small to detect differences.

The improvement of exercise capacity and skeletal muscle strength in RTx and HD patients after completion of the twelve-weeks lasting exercise program was found to coincide with significant improvements of self-reported health-related QoL, in particular in the domains related to physical functioning. Earlier studies in RTx and HD patients also reported exercise training to improve QoL[67,119,148,168,176].
Improvement of QoL and in particular improvement of the scores related to physical functioning, is especially important because the self-reported physical functioning scores are reported to be predictive of outcomes. The physical component scale (PCS) score of the SF-36 questionnaire is found to be a consistent, powerful predictor of morbidity and mortality in HD patients[169,173,177,178]. DeOreo et al.[169] have found the PCS to be a significant predictor of outcomes in HD patients: patients with PCS scores below the median (<34) were twice as likely to die and 1.5 times more likely to be hospitalized as patients with PCS scores at or above the median score. Moreover, the probability of survival increased approximately 10% with every five points increase of the PCS score.
QoL is also shown to be a predictor of survival in other patient populations, such as cancer patients, geriatric patients, and lung transplant recipients[179-184]. In RTx patients, the relationship between self-reported physical functioning and outcomes has not been established. It might be expected that improved QoL has beneficial effects on outcome in the RTx population too. Future research is needed to study this aspect.

It is not known whether the beneficial effects of the intensive exercise training on physical performance and QoL persisted after completion of the program and whether the program accomplished an altered life-style towards regular physical activity. Patients had the opportunity to continue exercise training once a week in a setting comparable to the training intervention. More than half of the patients did continue exercising for at least six months. Studies in other patient groups showed that patients may fail to adhere to improved exercise patterns after the supervised training period has terminated[185]. Many of the effects of both endurance and resistance training diminish within two weeks if physical activity is substantially reduced, and disappear within two to eight months if physical activity is not resumed[86]. Therefore, a long-term change in life-style in the field of physical activity is required to accomplish long-term improvements in exercise capacity, skeletal muscle strength, and QoL. This may be achieved by a stepwise approach of a short-term, intensive exercise training program to improve physical performance, followed by a maintenance

program and counseling. More research is needed to unravel strategies to maintain improvement in physical performance and QoL both in RTx and HD patients.

We included only stable RTx and HD patients without severe co-morbidity in the training study. Moreover, HD patients had to be on the waiting list for renal transplantation. We expect exercise training to have also beneficial effects on exercise capacity, muscle strength, and QoL in RTx and HD patients who do suffer from extensive co-morbidity, such as cardiovascular disease or diabetes mellitus. This expectation is based on the fact that exercise programs (consisting of cardiovascular endurance and strength training) are proven to be effective to improve the functional capacity and exercise tolerance, skeletal muscle strength, and self-perceived QoL in patients with chronic heart failure and diabetes mellitus[186-194]. In diabetes patients, exercise training could also induce positive adaptations on glucose control and insulin resistance. The poor general health status of RTx and HD patients suffering from severe co-morbidity probably causes the physical performance of these patients to be more affected as compared to patients without co-morbidity. Therefore, exercise training appears to be even more important in renal patients suffering from extensive co-morbidity as compared to those without co-morbidity.

To summarize, the results of the training intervention study clearly show that exercise training is feasible in both RTx and HD patients. Exercise training had beneficial effects on exercise capacity, skeletal muscle strength, and QoL. The response to training in both the RTx and HD patients was not significantly different compared to the response in sedentary, age-matched, healthy controls. Exercise training thus may be of great benefit, at least in the short term. Potential long-term benefits need to be addressed in future studies.

Risks of exercise

The most serious inherent risk of exercise in the RTx and HD population is a cardiac event, but the most common risk is musculoskeletal injury[195]. These risks are higher with high intensity exercise (such as exercise testing) than with submaximal exercise (such as exercise training). Moreover, the risks of exercise are higher in patients with cardiovascular co-morbidity and/or low levels of physical fitness.
An important finding of our training intervention study is that both RTx and HD patients are able to participate safely in an intensive, supervised exercise training program. Only two RTx patients (5.7%) and two HD patients (12.5%) did not fully complete the exercise program. However, nobody had to drop out because of musculoskeletal injuries, vascular access problems or hemo-

dynamic or other exercise-related complications. Measures we took to reduce the risk of exercise-related complications to a minimum were 1) extensive screening of the patients (in particular cardiovascular screening) before start of the intervention program, 2) a solid warming-up at the beginning of every exercise session and an adequate cool-down time at the end of each session, 3) supervising of the cycle, walk and lifting techniques, 4) gradually increasing the intensity of the exercise training, and 5) developing an individual training program for each subject based on their baseline level of functioning. These measures have to be considered to ensure the safety of such an intensive exercise training program.

Exercise training appears to be not detrimental to the kidney function of RTx patients. Training did not affect the renal function of the RTx patients studied in this thesis. Likewise, in the study by Poortmans et al.[196] no adverse effects of intensive physical exercise on glomerular filtration rate and proteinuria have been observed.

Thus, if the measures to minimize the risks associated with exercise (as mentioned above) are followed, the risks of exercise in RTx and HD patients -even in patients suffering from co-morbidity[195]- appear to be low. For most of the RTx and HD patients, the risk benefit ratio will fall in favor of exercise, with the vast majority of patients exposed to greater risk by not exercising.

Summary and conclusions of the thesis

Body weight increases significantly after renal transplantation. This weight gain is primarily due to an increase of body FM, which is most pronounced in the truncal region. In RTx recipients suffering from severe malnutrition at the time of transplantation - usually characterized by both FM and LBM depletion - weight gain is not necessarily a negative finding, as it might indicate an improvement in their nutritional state. However, the increasing prevalence of overweight and obesity in ESRD patients undergoing renal transplantation is a major point of concern, as these patients are at risk for even further weight gain after transplantation. Excessive weight gain - and in particular a significant increase of (abdominal) FM - has adverse effects on the cardiovascular risk profile (i.e., hyperlipidemia, hypertension, insulin resistance and post-transplant diabetes, and the metabolic syndrome) in RTx patients, which is of importance in view of the high cardiovascular morbidity and mortality in the RTx population. Moreover, the development of obesity after kidney transplantation is associated with decreased graft and patient survival rates. Ergo, obesity may have far-reaching consequences in RTx patients.

The post-transplant changes in body weight and body composition are a consequence of a multifactorial process, potential factors involved being the use of immunosuppressive agents, in particular the use of corticosteroids, changes in dietary intake, and lack of physical activity. Physical activity turns out to be the dominant factor affecting body composition in RTx patients. It is inversely related to body FM, and positively related to the percentage of LBM. Moreover, physical activity appears to be an important determinant of exercise capacity in RTx patients. However, physical activity levels in RTx patients remain low - even after successful transplantation - and are therefore an important cause of impaired exercise capacity and skeletal muscle strength. Exercise capacity and muscle strength in RTx patients are significantly lower compared to healthy, sedentary controls and are not significantly different compared to HD patients. These findings underscore the importance of exercise training and increasing physical activity levels in RTx patients.

Twice weekly intensive, standardized and supervised exercise training (consisting of a combination of endurance and resistance training) during a period of twelve weeks does not affect body weight and body composition, assessed by DEXA, in RTx and HD patients. In contrast, body weight did increase significantly in controls, in particular in males, due to a significant increase of the LBM. The use of corticosteroids does not appear to affect the response to training with regard to body FM or LBM in RTx patients.
Therefore, the exercise program used was not effective in the management of body weight and body FM in RTx patients. For weight and body FM reduction in the post-transplant period, a combination of exercise training and dietary intervention is probably more effective. Future studies are necessary to unravel the best strategy for post-transplant weight management. Increased levels of daily physical activity appear to be especially important in the *prevention* of excessive weight gain. Therefore, exercise training and accomplishing changes in life-style towards regular physical activity are needed in the earliest possible stages of chronic renal failure, i.e., in the pre-dialysis and dialysis period.

The intensive, supervised exercise training did have beneficial effects on exercise capacity and skeletal muscle strength in both RTx and HD patients. These effects coincided with a significant improvement of the self-reported health-related QoL. The use of low maintenance doses of corticosteroids does not appear to compromise the response to training in RTx patients. Interestingly, the proportional functional response (i.e., the response regarding exercise capacity and skeletal muscle strength) to the standardized exercise program did not differ in RTx patients, HD patients, and healthy, sedentary controls.

Exercise training has the potential to influence health status in HD patients by increasing exercise capacity, skeletal muscle strength and health-related QoL. In RTx patients, the beneficial effects of exercise training may prevent the development of new medical problems such as obesity, abnormalities in the lipid profile, post-transplant diabetes mellitus, and cardiovascular disease. Exercise training can reverse the negative spiral of deconditioning in HD and RTx patients. It is therefore of the utmost importance to pay more attention to exercise training and changes in life-style towards regular physical activity both in HD and RTx patients. For this, exercise training has to be considered as a structural part of the routine treatment of these patient groups. At present, too little attention is paid to exercise training in the care of the renal patient.

The costs of dialysis therapy amount to 50.000 - 60.000 euro per patient per year, whereas a renal transplantation costs approximately 60.000 euro and the life-long nephrological medical care after renal transplantation amounts to 10.000 euro per patient per year. The estimated costs of exercise training are negligible in relation to the overall health care and society costs for these patient groups. The potential benefits of exercise training in HD and RTx patients are great, and therefore, a relative small additional investment may well lead to considerable savings in the longer term. Although the short-term effectiveness of exercise training has been established, this intervention is not yet reimbursed. This is a barrier for implementation, since most patients cannot afford to pay for exercise training themselves. Long-term effectiveness and cost-effectiveness of exercise training need to be established to convince health care insurers that exercise training is efficient and should be routinely reimbursed.

References

1. Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol 1998; 9(11): 2135-2141.
2. McDonald SP, Russ GR. Survival of recipients of cadaveric kidney transplants compared with those receiving dialysis treatment in Australia and New Zealand, 1991-2001. Nephrol Dial Transplant 2002; 17(12):2212-2219.
3. Overbeck I, Bartels M, Decker O, Harms J, Hauss J, Fangmann J. Changes in quality of life after renal transplantation. Transplant Proc 2005; 37(3):1618-1621.
4. Fujisawa M, Ichikawa Y, Yoshiya K, Isotani S, Higuchi A, Nagano S, Arakawa S, Hamami G, Matsumoto O, Kamidono S. Assessment of health-related quality of life in renal transplant and hemodialysis patients using the SF-36 health survey. Urology 2000; 56(2):201-206.
5. Locatelli F, Fouque D, Heimburger O, Drueke TB, Cannata-Andia JB, Horl WH, Ritz E. Nutritional status in dialysis patients: a European consensus. Nephrol Dial Transplant 2002; 17(4):563-572.
6. Stenvinkel P. Malnutrition and chronic inflammation as risk factors for cardiovascular disease in chronic renal failure. Blood Purif 2001; 19(2):143-151.
7. Johansen KL. Exercise and chronic kidney disease: current recommendations. Sports Med 2005; 35(6):485-499.
8. Miller DG, Levine SE, D'Elia JA, Bistrian BR. Nutritional status of diabetic and nondiabetic patients after renal transplantation. Am J Clin Nutr 1986; 44(1):66-69.
9. Kempeneers G, Noakes TD, van Zyl-Smit R, Myburgh KH, Lambert M, Adams B, Wiggins T. Skeletal muscle limits the exercise tolerance of renal transplant recipients: effects of a graded exercise training program. Am J Kidney Dis 1990; 16(1):57-65.
10. Painter P, Hanson P, Messer-Rehak D, Zimmerman SW, Glass NR. Exercise tolerance changes following renal transplantation. Am J Kidney Dis 1987; 10(6):452-456.
11. Laville M, Fouque D. Nutritional aspects in hemodialysis. Kidney Int Suppl 2000; 76: S133-139.
12. Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome - the heart of the matter. Nephrol Dial Transplant 2002; 17 (Suppl 11):28-31.
13. Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA, Bergstrom J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant 2000; 15(7): 953-960.
14. Modlin CS, Flechner SM, Goormastic M, Goldfarb DA, Papajcik D, Mastroianni B, Novick AC. Should obese patients lose weight before receiving a kidney transplant? Transplantation 1997; 64(4):599-604.
15. Meier-Kriesche HU, Vaghela M, Thambuganipalle R, Friedman G, Jacobs M, Kaplan B. The effect of body mass index on long-term renal allograft survival. Transplantation 1999; 68(9):1294-1297.
16. Meier-Kriesche HU, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. Transplantation 2002; 73(1):70-74.
17. Halme L, Eklund B, Kyllonen L, Salmela K. Is obesity still a risk factor in renal transplantation? Transpl Int 1997; 10(4):284-288.
18. Raiss-Jalali GA, Mehdizadeh AR, Razmkon A, Rouzbeh J, Behzadi S, Memari H, Malek-Hosseini SA. Effect of body mass index at time of transplantation and weight gain after transplantation on allograft function in kidney transplant recipients in Shiraz. Transplant Proc 2005; 37(7):2998-3000.
19. Patel MG. The effect of dietary intervention on weight gains after renal transplantation. J Ren Nutr 1998; 8(3):137-141.

20. Nielens H, Lejeune TM, Lalaoui A, Squifflet JP, Pirson Y, Goffin E. Increase of physical activity level after successful renal transplantation: a 5 year follow-up study. Nephrol Dial Transplant 2001; 16(1):134-140.
21. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, Rocher LL, Campbell DA. Obesity and renal transplantation. Surg Gynecol Obstet 1991; 172(5):367-376.
22. Baum CL, Thielke K, Westin E, Kogan E, Cicalese L, Benedetti E. Predictors of weight gain and cardiovascular risk in a cohort of racially diverse kidney transplant recipients. Nutrition 2002; 18(2):139-146.
23. Rogers CC, Alloway RR, Buell JF, Boardman R, Alexander JW, Cardi M, Roy-Chaudhury P, First MR, Succop P, Munda R, Woodle ES, Hanaway M. Body weight alterations under early corticosteroid withdrawal and chronic corticosteroid therapy with modern immuno-suppression. Transplantation 2005; 80(1):26-33.
24. Drafts HH, Anjum MR, Wynn JJ, Mulloy LL, Bowley JN, Humphries AL. The impact of pre-transplant obesity on renal transplant outcomes. Clin Transplant 1997; 11(5 Pt 2):493-496.
25. Clunk JM, Lin CY, Curtis JJ. Variables affecting weight gain in renal transplant recipients. Am J Kidney Dis 2001; 38(2):349-353.
26. Johnson CP, Gallagher-Lepak S, Zhu YR, Porth C, Kelber S, Roza AM, Adams MB. Factors influencing weight gain after renal transplantation. Transplantation 1993; 56(4):822-827.
27. El-Agroudy AE, Wafa EW, Gheith OE, Shehab el-Dein AB, Ghoneim MA. Weight gain after renal transplantation is a risk factor for patient and graft outcome. Transplantation 2004; 77(9):1381-1385.
28. Micozkadioglu H, Ozdemir FN, Sezer S, Arat Z, Haberal M. Weight gain after living-related renal transplantation affects long-term graft function. Transplant Proc 2005; 37(2):1029-1032.
29. Stengel B, Billon S, Van Dijk PC, Jager KJ, Dekker FW, Simpson K, Briggs JD. Trends in the incidence of renal replacement therapy for end-stage renal disease in Europe, 1990-1999. Nephrol Dial Transplant 2003; 18(9):1824-1833.
30. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases. US Renal Data System. The 2005 USRDS Annual Data Report: Atlas of End-Stage Renal Disease in The United States, 2005.
31. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. JAMA 1999; 282(16):1519-1522.
32. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001; 286(10):1195-1200.
33. National Dutch Registry of Patients on Renal Replacement Therapy (RENINE), 2005.
34. French SA, Story M, Jeffery RW. Environmental influences on eating and physical activity. Annu Rev Public Health 2001; 22:309-335.
35. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Hooff JP. Weight changes after renal transplantation: a comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immunosuppressive therapy. Transpl Int 2003; 16(5): 300-306.
36. van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP. Post-transplantation weight gain is predominantly due to an increase in body fat mass. Transplantation 2000; 70(1):241-242.
37. Yanovski JA, Cutler GB Jr. Glucocorticoid action and the clinical features of Cushing's syndrome. Endocrinol Metab Clin North Am 1994; 23(3):487-509.
38. Danovitch GM. Immunosuppressive medications and protocols for kidney transplantation, in Handbook of kidney transplantation. Danovitch GM, Editor. Little Brown and Compagny, Boston. 1992:67-104.
39. Langone AJ, Harold Helderman J. Immunosuppression, in Medical Management of Kidney Transplantation. Weir MR, Editor. Lippincott Williams & Wilkins, Philadelphia. 2005:127-137.
40. Ratcliffe PJ, Dudley CR, Higgins RM, Firth JD, Smith B, Morris PJ. Randomised controlled trial of steroid withdrawal in renal transplant recipients receiving triple immunosuppression. Lancet 1996; 348(9028):643-648.
41. Massy ZA, Kasiske BL. Post-transplant hyperlipidemia: mechanisms and management. J Am Soc Nephrol 1996; 7(7):971-977.

42. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. J Am Soc Nephrol 1996; 7(1):158-165.
43. Pirsch JD, D'Alessandro AM, Sollinger HW, Knechtle SJ, Reed A, Kalayoglu M, Belzer FO. Hyperlipidemia and transplantation: etiologic factors and therapy. J Am Soc Nephrol 1992; 2(Suppl 12):S238-242.
44. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990; 51(6): 1106-1112.
45. Lohman TG. Dual energy x-ray absorptiometry, in Human body composition. Roche AF, Heimsfield SB, Lohman TG, Editors. Human Kinetics, Champaign. 1996:63-78.
46. Jensen MD, Kanaley JA, Reed JE, Sheedy PF. Measurement of abdominal and visceral fat with computed tomography and dual-energy x-ray absorptiometry. Am J Clin Nutr 1995; 61(2):274-278.
47. Kamel EG, McNeill G, Han TS, Smith FW, Avenell A, Davidson L, Tothill P. Measurement of abdominal fat by magnetic resonance imaging, dual-energy X-ray absorptiometry and anthropometry in non-obese men and women. Int J Obes Relat Metab Disord 1999; 23(7):686-692.
48. Kamel EG, McNeill G, Van Wijk MC. Change in intra-abdominal adipose tissue volume during weight loss in obese men and women: correlation between magnetic resonance imaging and anthropometric measurements. Int J Obes Relat Metab Disord 2000; 24(5):607-613.
49. Gotfredsen A, Jensen J, Borg J, Christiansen C. Measurement of lean body mass and total body fat using dual photon absorptiometry. Metabolism 1986; 35(1):88-93.
50. Bhatla B, Moore H, Emerson P, Keshaviah P, Prowant B, Nolph KD, Singh A. Lean body mass estimation by creatinine kinetics, bioimpedance, and dual energy x-ray absorptiometry in patients on continuous ambulatory peritoneal dialysis. ASAIO J 1995; 41(3):M442-446.
51. Hart PD, Wilkie ME, Edwards A, Cunningham J. Dual energy X-ray absorptiometry versus skinfold measurements in the assessment of total body fat in renal transplant recipients. Eur J Clin Nutr 1993; 47(5):347-352.
52. Kerr PG, Strauss BJ, Atkins RC. Assessment of the nutritional state of dialysis patients. Blood Purif 1996; 14(5):382-387.
53. Heimburger O, Qureshi AR, Blaner WS, Berglund L, Stenvinkel P. Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. Am J Kidney Dis 2000; 36(6):1213-1225.
54. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am J Kidney Dis 2000; 35(6 Suppl 2):S1-140.
55. Tothill P, Nord RH. Limitations of dual-energy x-ray absorptiometry. Am J Clin Nutr 1995; 61(2):398-400.
56. Horber FF, Thomi F, Casez JP, Fonteille J, Jaeger P. Impact of hydration status on body composition as measured by dual energy X-ray absorptiometry in normal volunteers and patients on haemodialysis. Br J Radiol 1992; 65(778):895-900.
57. Abrahamsen B, Hansen TB, Hogsberg IM, Pedersen FB, Beck-Nielsen H. Impact of hemodialysis on dual X-ray absorptiometry, bioelectrical impedance measurements, and anthropometry. Am J Clin Nutr 1996; 63(1):80-86.
58. Going SB, Massett MP, Hall MC, Bare LA, Root PA, Williams DP, Lohman TG. Detection of small changes in body composition by dual-energy x-ray absorptiometry. Am J Clin Nutr 1993; 57(6):845-850.
59. Lands LC, Hornby L, Hohenkerk JM, Glorieux FH. Accuracy of measurements of small changes in soft-tissue mass by dual-energy x-ray absorptiometry. Clin Invest Med 1996; 19(4):279-285.
60. van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry. J Am Soc Nephrol 1999; 10(5):1067-1079.
61. Schoeller DA. Hydrometry, in Human body composition. Roche AF, Heymsfield SB, Lohman TG, Editors. Human Kinetics, Champaign, IL. 1996:25-44.

62. Cox-Reijven PL, Kooman JP, Soeters PB, van der Sande FM, Leunissen KM. Role of bioimpedance spectroscopy in assessment of body water compartments in hemodialysis patients. Am J Kidney Dis 2001; 38(4):832-838.
63. Isiklar I, Akin O, Demirag A, Niron EA. Effects of renal transplantation on body composition. Transplant Proc 1998; 30(3):831-832.
64. Ulivieri FM, Piodi LP, Aroldi A, Cesana BM. Effect of kidney transplantation on bone mass and body composition in males. Transplantation 2002; 73(4):612-615.
65. Kayacan SM, Yildiz A, Kazancioglu R, Sahin S, Sever MS, Ark E. The changes in serum leptin, body fat mass and insulin resistance after renal transplantation. Clin Transplant 2003; 17(1):63-68.
66. Painter PL, Topp KS, Krasnoff JB, Adey D, Strasner A, Tomlanovich S, Stock P. Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients. Kidney Int 2003; 63(6):2309-2316.
67. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich S, Ascher NL. A randomized trial of exercise training after renal transplantation. Transplantation 2002; 74(1):42-48.
68. Steiger U, Lippuner K, Jensen EX, Montandon A, Jaeger P, Horber FF. Body composition and fuel metabolism after kidney grafting. Eur J Clin Invest 1995; 25(11):809-816.
69. van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation 2000; 69(8):1591-1598.
70. Forbes GB. Body composition: influence of nutrition, disease, growth and aging, in Modern nutrition in health and disease. Shils ME, Olson JA, Shike M, Editors. Lea & Febiger, Philadelphia. 1994:781-801.
71. Bjorntorp P. Obesity and the risk of cardiovascular disease. Ann Clin Res 1985; 17(1):3-9.
72. Oosterlee A, Doornbos G, Seidell J. Vetverdeling in samenhang met risico-indicatoren voor hart- en vaatziekten. T Soc Gezondheidszorg 1987; 65:90-95.
73. Rebuffe-Scrive M, Krotkiewski M, Elfverson J, Bjorntorp P. Muscle and adipose tissue morphology and metabolism in Cushing's syndrome. J Clin Endocrinol Metab 1988; 67(6):1122-1128.
74. Bjorntorp P, Ottorson M, Rebuffe-Scrive M. Regional obesity and steroid hormone interactions in human adipose tissue, in Obesity: Towards a molecular approach. Bray G, Ricquier D, Spiegelman B, Editors. UCLA Symposia, New York. 1990:411-454.
75. Mathieu RL, Casez JP, Jaeger P, Montandon A, Peheim E, Horber FF. Altered body composition and fuel metabolism in stable kidney transplant patients on immuno-suppressive monotherapy with cyclosporine A. Eur J Clin Invest 1994; 24(3):195-200.
76. Peeke PM, Chrousos GP. Hypercortisolism and obesity. Ann N Y Acad Sci 1995; 771: 665-676.
77. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Evidence that prednisone-induced myopathy is reversed by physical training. J Clin Endocrinol Metab 1985; 61(1):83-88.
78. Horber FF, Scheidegger JR, Grunig BE, Frey FJ. Thigh muscle mass and function in patients treated with glucocorticoids. Eur J Clin Invest 1985; 15(6):302-307.
79. Horber FF, Zurcher RM, Herren H, Crivelli MA, Robotti G, Frey FJ. Altered body fat distribution in patients with glucocorticoid treatment and in patients on long-term dialysis. Am J Clin Nutr 1986; 43(5):758-769.
80. van den Ham ECH, Kooman JP, Christiaans ML, van Hooff JP. The influence of early steroid withdrawal on body composition and bone mineral density in renal transplantation patients. Transpl Int 2003; 16(2):82-87.
81. Food and Nutrition Council of The Netherlands. Dietary Reference Intakes 1989. The Hague, 1992.
82. Rocco MV, Paranandi L, Burrowes JD, Cockram DB, Dwyer JT, Kusek JW, Leung J, Makoff R, Maroni B, Poole D. Nutritional status in the HEMO Study cohort at baseline. Hemodialysis. Am J Kidney Dis 2002; 39(2):245-256.
83. Steiber AL. Clinical indicators associated with poor oral intake of patients with chronic renal failure. J Ren Nutr 1999; 9(2):84-88.

84. El Haggan W, Vendrely B, Chauveau P, Barthe N, Castaing F, Berger F, de Precigout V, Potaux L, Aparicio M. Early evolution of nutritional status and body composition after kidney transplantation. Am J Kidney Dis 2002; 40(3):629-637.
85. Lopes IM, Martin M, Errasti P, Martinez JA. Benefits of a dietary intervention on weight loss, body composition, and lipid profile after renal transplantation. Nutrition 1999; 15(1):7-10.
86. Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention. JAMA 1996; 276(7):522.
87. Watts K, Jones TW, Davis EA, Green D. Exercise training in obese children and adolescents: current concepts. Sports Med 2005; 35(5):375-392.
88. Andersen LB, Schnohr P, Schroll M, Hein HO. All-cause mortality associated with physical activity during leisure time, work, sports, and cycling to work. Arch Intern Med 2000; 160(11):1621-1628.
89. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med 1986; 314(10):605-613.
90. Morris JN, Everitt MG, Pollard R, Chave SP, Semmence AM. Vigorous exercise in leisure-time: protection against coronary heart disease. Lancet 1980; 2(8206):1207-1210.
91. Wilmore JH. Increasing physical activity: alterations in body mass and composition. Am J Clin Nutr 1996; 63(Suppl 3):S456-460.
92. Wilmore JH. Body composition in sport and exercise: directions for future research. Med Sci Sports Exerc 1983; 15(1):21-31.
93. Epstein LH, Wing RR. Aerobic exercise and weight. Addict Behav 1980; 5(4):371-388.
94. Ballor DL, Keesey RE. A meta-analysis of the factors affecting exercise-induced changes in body mass, fat mass and fat-free mass in males and females. Int J Obes 1991; 15(11): 717-726.
95. Westerterp KR. Alterations in energy balance with exercise. Am J Clin Nutr 1998; 68(4): S970-974.
96. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. Ann Intern Med 2000; 133(2):92-103.
97. Ross R, Janssen I, Dawson J, Kungl AM, Kuk JL, Wong SL, Nguyen-Duy TB, Lee S, Kilpatrick K, Hudson R. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obes Res 2004; 12(5):789-798.
98. Wilmore JH, Despres JP, Stanforth PR, Mandel S, Rice T, Gagnon J, Leon AS, Rao D, Skinner JS, Bouchard C. Alterations in body weight and composition consequent to 20 wk of endurance training: the HERITAGE Family Study. Am J Clin Nutr 1999; 70(3):346-352.
99. Blair SN. Evidence for success of exercise in weight loss and control. Ann Intern Med 1993; 119(7 Pt 2):702-706.
100. Kohrt WM, Malley MT, Dalsky GP, Holloszy JO. Body composition of healthy sedentary and trained, young and older men and women. Med Sci Sports Exerc 1992; 24(7):832-837.
101. Painter PL, Luetkemeier MJ, Moore GE, Dibble SL, Green GA, Myll JO, Carlson LL. Health-related fitness and quality of life in organ transplant recipients. Transplantation 1997; 64(12):1795-1800.
102. Johansen KL, Chertow GM, Ng AV, Mulligan K, Carey S, Schoenfeld PY, Kent-Braun JA. Physical activity levels in patients on hemodialysis and healthy sedentary controls. Kidney Int 2000; 57(6):2564-2570.
103. Majchrzak KM, Pupim LB, Chen K, Martin CJ, Gaffney S, Greene JH, Ikizler TA. Physical activity patterns in chronic hemodialysis patients: comparison of dialysis and nondialysis days. J Ren Nutr 2005; 15(2):217-224.
104. Moons P, Vanrenterghem Y, van Hooff JP, Squifflet JP, Margodt D, Mullens M, Thevissen I, de Geest S. Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multicentre study. Transpl Int 2003; 16(9):653-664.
105. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37(12):1595-1607.
106. McFarlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. J Clin Endocrinol Metab 2001; 86(2):713-718.

107. Marques-Vidal P, Mazoyer E, Bongard V, Gourdy P, Ruidavets JB, Drouet L, Ferrieres J. Prevalence of insulin resistance syndrome in southwestern France and its relationship with inflammatory and hemostatic markers. Diabetes Care 2002; 25(8):1371-1377.
108. Chan JC, Cheung JC, Stehouwer CD, Emeis JJ, Tong PC, Ko GT, Judkin JS. The central roles of obesity-associated dyslipidaemia, endothelial activation and cytokines in the Metabolic Syndrome - an analysis by structural equation modelling. Int J Obes Relat Metab Disord 2002; 26(7):994-1008.
109. Lewinter MM. Association of syndromes of insulin resistance with coronary artery disease. Coron Artery Dis 2005; 16(8):477-480.
110. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an american heart association/national heart, lung, and blood institute scientific statement: executive summary. Circulation 2005; 112(17):2735-2752.
111. de Vries AP, Bakker SJ, van Son WJ, Homan van der Heide JJ, The TH, de Jong PE, Gans RO. Insulin resistance as putative cause of chronic renal transplant dysfunction. Am J Kidney Dis 2003; 41(4):859-867.
112. de Vries AP, Bakker SJ, van Son WJ, van der Heide JJ, Ploeg RJ, The HT, de Jong PE, Gans RO. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. Am J Transplant 2004; 4(10):1675-1683.
113. Shoji T, Nishizawa Y. Chronic kidney disease as a metabolic syndrome with malnutrition - need for strict control of risk factors. Intern Med 2005; 44(3):179-187.
114. Hjelmesaeth J, Hartmann A, Midtvedt K, Aakhus S, Stenstrom J, Morkrid L, Egeland T, Tordarson H, Fauchald P. Metabolic cardiovascular syndrome after renal transplantation. Nephrol Dial Transplant 2001; 16(5):1047-1052.
115. Lo A, Culbreath B, Egidi MF, Cashion A, Gaber OA. Metabolic complications pre and post renal transplantation. Am J Transplant 2004; 4(S8):546.
116. Lo A, Pharm D. Immunosuppression and metabolic syndrome in renal transplant recipients. Metabolic Syndrome and Related Disorders 2004; 2(4):263-273.
117. Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ. Principles of exercise testing and interpretation. Lippincott Williams and Wilkins, Baltimore. 1999.
118. Huang Y, Macera CA, Blair SN, Brill PA, Kohl HW, Kronenfeld JJ. Physical fitness, physical activity, and functional limitation in adults aged 40 and older. Med Sci Sports Exerc 1998; 30(9):1430-1435.
119. Painter P, Carlson L, Carey S, Paul SM, Myll J. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis 2000; 35(3):482-492.
120. Johansen KL. Physical functioning and exercise capacity in patients on dialysis. Adv Ren Replace Ther 1999; 6(2):141-148.
121. Painter P. The importance of exercise training in rehabilitation of patients with end-stage renal disease. Am J Kidney Dis 1994; 24(1 Suppl 1):S2-9; discussion S31-32.
122. Goldberg AP, Geltman EM, Hagberg JM, Gavin JR, Delmez JA, Carney RM, Naumowicz A, Oldfield MH, Harter HR. Therapeutic benefits of exercise training for hemodialysis patients. Kidney Int Suppl 1983; 16:S303-309.
123. Painter P, Messer-Rehak D, Hanson P, Zimmerman SW, Glass NR. Exercise capacity in hemodialysis, CAPD, and renal transplant patients. Nephron 1986; 42(1):47-51.
124. Painter PL, Nelson-Worel JN, Hill MM, Thornbery DR, Shelp WR, Harrington AR, Weinstein AB. Effects of exercise training during hemodialysis. Nephron 1986; 43(2):87-92.
125. Zabetakis PM, Gleim GW, Pasternack FL, Saraniti A, Nicholas JA, Michelis MF. Long-duration submaximal exercise conditioning in hemodialysis patients. Clin Nephrol 1982; 18(1):17-22.
126. Diesel W, Noakes TD, Swanepoel C, Lambert M. Isokinetic muscle strength predicts maximum exercise tolerance in renal patients on chronic hemodialysis. Am J Kidney Dis 1990; 16(2):109-114.

127. Lundin AP, Akerman MJ, Chesler RM, Delano BG, Goldberg N, Stein RA, Friedman EA. Exercise in hemodialysis patients after treatment with recombinant human erythropoietin. Nephron 1991; 58(3):315-319.
128. Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH. Uremic myopathy limits aerobic capacity in hemodialysis patients. Am J Kidney Dis 1993; 22(2): 277-287.
129. Sietsema KE, Hiatt WR, Esler A, Adler S, Amato A, Brass EP. Clinical and demographic predictors of exercise capacity in end-stage renal disease. Am J Kidney Dis 2002; 39(1): 76-85.
130. Painter P, Moore G, Carlson L, Paul S, Myll J, Phillips W, Haskell W. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. Am J Kidney Dis 2002; 39(2):257-265.
131. Violan MA, Pomes T, Maldonado S, Roura G, De la Fuente I, Verdaguer T, Lloret R, Torregrosa JV, Campistol JM. Exercise capacity in hemodialysis and renal transplant patients. Transplant Proc 2002; 34(1):417-418.
132. Hansen JE. Exercise instruments, schemes, and protocols for evaluating the dyspneic patient. Am Rev Respir Dis 1984; 129(2 Pt 2):S25-27.
133. Janicki JS, Weber KT, McElroy PA. Use of the cardiopulmonary exercise test to evaluate the patient with chronic heart failure. Eur Heart J 1988; 9(Suppl H):55-58.
134. van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Franssen FM, Akkermans MA, Janssen PP, van Hooff JP. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. Am J Transplant 2005; 5(8):1957-1965.
135. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Canadian Erythropoietin Study Group. BMJ 1990; 300(6724):573-578.
136. Moreno F, Lopez Gomez JM, Sanz-Guajardo D, Jofre R, Valderrabano F. Quality of life in dialysis patients. A spanish multicentre study. Spanish Cooperative Renal Patients Quality of Life Study Group. Nephrol Dial Transplant 1996; 11(Suppl 2):S125-129.
137. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 1996; 153(3):976-980.
138. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation 1992; 85(5):1751-1759.
139. Magnusson G, Kaijser L, Rong H, Isberg B, Sylven C, Saltin B. Exercise capacity in heart failure patients: relative importance of heart and skeletal muscle. Clin Physiol 1996; 16(2):183-195.
140. King AC, Tribble DL. The role of exercise in weight regulation in nonathletes. Sports Med 1991; 11(5):331-349.
141. Macdonald JH, Marcora SM, Jibani M, Phanish MK, Holly J, Lemmey AB. Intradialytic exercise as anabolic therapy in haemodialysis patients - a pilot study. Clin Physiol Funct Imaging 2005; 25(2):113-118.
142. Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Tourkantonis A, Deligiannis A. The effects of exercise training on muscle atrophy in haemodialysis patients. Nephrol Dial Transplant 1998; 13(3):685-699.
143. Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, Fielding RA, Roubenoff R, Singh MF. Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency. A randomized, controlled trial. Ann Intern Med 2001; 135(11):965-976.
144. Miller TD, Squires RW, Gau GT, Ilstrup DM, Frohnert PP, Sterioff S. Graded exercise testing and training after renal transplantation: a preliminary study. Mayo Clin Proc 1987; 62(9): 773-777.
145. Koufaki P, Mercer TH, Naish PF. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. Clin Physiol Funct Imaging 2002; 22(2): 115-124.

146. Headley S, Germain M, Mailloux P, Mulhern J, Ashworth B, Burris J, Brewer B, Nindl B, Coughlin M, Welles R, Jones M. Resistance training improves strength and functional measures in patients with end-stage renal disease. Am J Kidney Dis 2002; 40(2):355-364.
147. DePaul V, Moreland J, Eager T, Clase CM. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am J Kidney Dis 2002; 40(6):1219-1229.
148. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. Nephrol Dial Transplant 2005; 20(1):141-146.
149. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002; 346(11):793-801.
150. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. N Engl J Med 1988; 319(21):1379-1384.
151. Blair SN, Kohl HW, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 1989; 262(17):2395-2401.
152. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, Fowler MB. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. Ann Intern Med 1998; 129(4):286-293.
153. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 1992; 327(25):1785-1788.
154. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. Am J Respir Crit Care Med 2003; 167(4):544-549.
155. Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. Kidney Int 2004; 65(2):719-724.
156. Painter PL, Hector L, Ray K, Lynes L, Paul SM, Dodd M, Tomlanovich SL, Ascher NL. Effects of exercise training on coronary heart disease risk factors in renal transplant recipients. Am J Kidney Dis 2003; 42(2):362-369.
157. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000; 356(9224):147-152.
158. Kasiske BL, Chakkera HA, Roel J. Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol 2000; 11(9):1735-1743.
159. Ware J. SF-36 Health Survey: Manual and Interpretation Guide. The Health Institute, Boston. 1993.
160. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med 1996; 334(13):835-840.
161. Franke GH, Reimer J, Kohnle M, Luetkes P, Maehner N, Heemann U. Quality of life in end-stage renal disease patients after successful kidney transplantation: development of the ESRD symptom checklist - transplantation module. Nephron 1999; 83(1):31-39.
162. Gomez-Besteiro MI, Santiago-Perez MI, Alonso-Hernandez A, Valdes-Canedo F, Rebollo-Alvarez P. Validity and reliability of the SF-36 questionnaire in patients on the waiting list for a kidney transplant and transplant patients. Am J Nephrol 2004; 24(3):346-351.
163. Johansen KL, Painter P, Kent-Braun JA, Ng AV, Carey S, Da Silva M, Chertow GM. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. Kidney Int 2001; 59(3):1121-1127.
164. Cleemput I, Kesteloot K, Moons P, Vanrenterghem Y, van Hooff JP, Squifflet JP, De Geest S. The construct and concurrent validity of the EQ-5D in a renal transplant population. Value Health 2004; 7(4):499-509.
165. Kato A, Odamaki M, Yamamoto T, Yonemura K, Maruyama Y, Kumagai H, Hishida A. Influence of body composition on 5 year mortality in patients on regular haemodialysis. Nephrol Dial Transplant 2003; 18(2):333-340.

166. Kaysen GA, Chertow GM, Adhikarla R, Young B, Ronco C, Levin NW. Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. Kidney Int 2001; 60(1):333-340.
167. Kaysen GA, Eiserich JP. Characteristics and effects of inflammation in end-stage renal disease. Semin Dial 2003; 16(6):438-446.
168. Painter P, Carlson L, Carey S, Paul SM, Myll J. Low-functioning hemodialysis patients improve with exercise training. Am J Kidney Dis 2000; 36(3):600-608.
169. DeOreo PB. Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. Am J Kidney Dis 1997; 30(2):204-212.
170. Tawney KW, Tawney PJ, Hladik G, Hogan SL, Falk RJ, Weaver C, Moore DT, Lee MY. The life readiness program: a physical rehabilitation program for patients on hemodialysis. Am J Kidney Dis 2000; 36(3):581-591.
171. Witzke O, Becker G, Franke G, Binek M, Philipp T, Heemann U. Kidney transplantation improves quality of life. Transplant Proc 1997; 29(1-2):1569-1570.
172. Russell JD, Beecroft ML, Ludwin D, Churchill DN. The quality of life in renal transplantation - a prospective study. Transplantation 1992; 54(4):656-660.
173. Matas AJ, McHugh L, Payne WD, Wrenshall LE, Dunn DL, Gruessner RW, Sutherland DE, Najarian JS. Long-term quality of life after kidney and simultaneous pancreas-kidney transplantation. Clin Transplant 1998; 12(3):233-242.
174. Shield CF, McGrath MM, Goss TF. Assessment of health-related quality of life in kidney transplant patients receiving tacrolimus (FK506)-based versus cyclosporine-based immunosuppression. FK506 Kidney Transplant Study Group. Transplantation 1997; 64(12):1738-1743.
175. Tsuji-Hayashi Y, Fukuhara S, Green J, Takai I, Shinzato T, Uchida K, Oshima S, Yamazaki C, Maeda K. Health-related quality of life among renal-transplant recipients in Japan. Transplantation 1999; 68(9):1331-1335.
176. Levendoglu F, Altintepe L, Okudan N, Ugurlu H, Gokbel H, Tonbul Z, Guney I, Turk S. A twelve week exercise program improves the psychological status, quality of life and work capacity in hemodialysis patients. J Nephrol 2004; 17(6):826-832.
177. Lowrie EG, Curtin RB, LePain N, Schatell D. Medical outcomes study short form-36: a consistent and powerful predictor of morbidity and mortality in dialysis patients. Am J Kidney Dis 2003; 41(6):1286-1292.
178. Knight EL, Ofsthun N, Teng M, Lazarus JM, Curhan GC. The association between mental health, physical function, and hemodialysis mortality. Kidney Int 2003; 63(5):1843-1851.
179. Fang FM, Tsai WL, Chiu HC, Kuo WR, Hsiung CY. Quality of life as a survival predictor for esophageal squamous cell carcinoma treated with radiotherapy. Int J Radiat Oncol Biol Phys 2004; 58(5):1394-1404.
180. Roychowdhury DF, Hayden A, Liepa AM. Health-related quality-of-life parameters as independent prognostic factors in advanced or metastatic bladder cancer. J Clin Oncol 2003; 21(4):673-678.
181. Applegate WB, Miller ST, Graney MJ, Elam JT, Burns R, Akins DE. A randomized, controlled trial of a geriatric assessment unit in a community rehabilitation hospital. N Engl J Med 1990; 322(22):1572-1578.
182. Forli L, Moum T, Bjortuft O, Vatn M, Boe J. The influence of underweight and dietary support on well-being in lung transplant candidates. Respir Med 2006; 100(7):1239-1246.
183. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 1995; 122(11):823-832.
184. Squier HC, Ries AL, Kaplan RM, Prewitt LM, Smith CM, Kriett JM, Jamieson SW. Quality of well-being predicts survival in lung transplantation candidates. Am J Respir Crit Care Med 1995; 152(6 Pt 1):2032-2036.
185. Graham H. A conceptual map for studying long-term exercise adherence in a cardiac population. Rehabil Nurs 2003; 28(3):80-86.

186. Rees K, Taylor RS, Singh S, Coats AJ, Ebrahim S. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev 2004; 3:CD003331.
187. Meyer K. Exercise training in heart failure: recommendations based on current research. Med Sci Sports Exerc 2001; 33(4):525-531.
188. Meyer T, Kindermann M, Kindermann W. Exercise programmes for patients with chronic heart failure. Sports Med 2004; 34(14):939-954.
189. Collins E, Langbein WE, Dilan-Koetje J, Bammert C, Hanson K, Reda D, Edwards L. Effects of exercise training on aerobic capacity and quality of life in individuals with heart failure. Heart Lung 2004; 33(3):154-161.
190. Koukouvou G, Kouidi E, Iacovides A, Konstantinidou E, Kaprinis G, Deligiannis A. Quality of life, psychological and physiological changes following exercise training in patients with chronic heart failure. J Rehabil Med 2004; 36(1):36-41.
191. Delagardelle C, Feiereisen P. Strength training for patients with chronic heart failure. Eura Medicophys 2005; 41(1):57-65.
192. Delagardelle C, Feiereisen P, Autier P, Shita R, Krecke R, Beissel J. Strength/endurance training versus endurance training in congestive heart failure. Med Sci Sports Exerc 2002; 34(12):1868-1872.
193. Tokmakidis SP, Zois CE, Volaklis KA, Kotsa K, Touvra AM. The effects of a combined strength and aerobic exercise program on glucose control and insulin action in women with type 2 diabetes. Eur J Appl Physiol 2004; 92(4-5):437-442.
194. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes Res Clin Pract 2002; 56(2):115-123.
195. Copley JB, Lindberg JS. The risks of exercise. Adv Ren Replace Ther 1999; 6(2):165-171.
196. Poortmans JR, Hermans L, Vandervliet A, Niset G, Godefroid C. Renal responses to exercise in heart and kidney transplant patients. Transpl Int 1997; 10(4):323-327.

Samenvatting

Samenvatting

De nieren spelen een zeer belangrijke rol bij de regulering van het volume en de samenstelling van de lichaamsvloeistoffen. Bij een verminderde nierfunctie ontstaan veranderingen in het interne milieu, zoals verstoringen in de vochtbalans, accumulatie van afvalstoffen (uremische toxinen) en verstoringen in de zuur-base- en electrolytenhuishouding. Bij patiënten met ernstig nierfalen is behandeling met een nierfunctievervangende therapie noodzakelijk om te kunnen overleven. De belangrijkste vormen van nierfunctievervangende therapie zijn dialyse (hemodialyse (HD) of peritoneaal dialyse (PD)) en niertransplantatie.

Dialyse corrigeert de verstoringen in het interne milieu van patiënten met een terminale nierinsufficiëntie slechts ten dele. Uremische complicaties, zoals vochtophoping, hypertensie, anemie, verstoringen in het calciumfosfaatmetabolisme en accumulatie van uremische toxinen, kunnen dus ontstaan. Het mortaliteitsrisico van dialysepatiënten is sterk verhoogd ten opzichte van patiënten zonder nierziekten. De vijfjaarsoverleving is 35-60%. De belangrijkste oorzaken van morbiditeit en mortaliteit bij dialysepatiënten zijn cardiovasculaire ziekten (hart- en vaatziekten), ondervoeding en chronische inflammatie. Deze complicaties zijn deels inherent aan het nierlijden zelf en deels aan de dialysebehandeling.

Na een succesvolle niertransplantatie verdwijnen de meeste uremische complicaties die geassocieerd zijn met terminale nierinsufficiëntie. De nierfunctie van een transplantatiepatiënt blijft echter ook na een geslaagde niertransplantatie subnormaal. Om de kans op afstoting van de getransplanteerde nier te verminderen, zijn niertransplantatiepatiënten (NTx-patiënten) hun hele leven lang afhankelijk van immunosuppressieve therapie (medicatie die het afweersysteem onderdrukt en daarmee afstoting van de nier moet voorkomen). Als gevolg van deze therapie is er een verhoogde kans op het ontstaan van infecties. Daarnaast kent de immunosuppressieve medicatie -zoals bijvoorbeeld calcineurine-inhibitoren (tacrolimus en cyclosporine) en corticosteroïden- veel bijwerkingen, zoals onder andere diabetes mellitus, tandvleeshypertrofie, hyperlipidemie, hypertensie, osteoporose en toename van het lichaamsgewicht. Toch verbetert de kwaliteit van leven na een geslaagde niertransplantatie en neemt de levensverwachting toe. De vijfjaarsoverleving van ontvangers van een postmortale donornier bedraagt ongeveer 71-74%, die van ontvangers van een levende donornier ongeveer 77-92%. Niertransplantatie is bovendien een kosteneffectieve behandelmodaliteit ten opzichte van dialyse. Dit alles maakt dat niertransplantatie op dit

moment dé voorkeursbehandeling is voor de overgrote meerderheid van patiënten met een terminale nierinsufficiëntie.

Ondervoeding en inspanningsintolerantie komen zeer frequent voor bij dialysepatiënten. Algemeen wordt aangenomen dat de voedingstoestand en de inspanningscapaciteit verbeteren na een geslaagde niertransplantatie. Er zijn echter weinig gegevens bekend over de veranderingen in lichaamssamenstelling en inspanningscapaciteit na niertransplantatie en over de determinanten van deze parameters bij transplantatiepatiënten.
In dit proefschrift zijn de veranderingen in lichaamsgewicht en lichaamssamenstelling na niertransplantatie en de potentiële determinanten van deze veranderingen bestudeerd. Om de (veranderingen in) lichaamssamenstelling bij NTx-patiënten vast te kunnen stellen, dienen betrouwbare, nauwkeurige methodieken gebruikt te worden. Omdat er geen gouden standaard voorhanden is om de lichaamssamenstelling van deze specifieke patiëntengroep te meten, zijn verschillende methodieken die gebruikt kunnen worden om de lichaamssamenstelling te bepalen, onderzocht en vergeleken in NTx-patiënten. Daarnaast is bestudeerd in hoeverre de inspanningscapaciteit en spierkracht van NTx-patiënten verschilt van die van HD-patiënten en gezonde controlepersonen. Ook zijn de potentiële determinanten van het verminderde fysieke functioneren en de slechte lichamelijke conditie van NTx-patiënten in kaart gebracht. Tot slot zijn de effecten van inspanningstraining op de lichaamssamenstelling en de lichamelijke conditie bestudeerd en vergeleken in NTx-patiënten, HD-patiënten en gezonde controlepersonen.

In **hoofdstuk 2** zijn de veranderingen in lichaamsgewicht na niertransplantatie bestudeerd in een cohort stabiele transplantatiepatiënten dat een relatief lage onderhoudsdosering steroïden gebruikte (0 mg of 5 mg per dag). Ook is de relatie tussen potentiële determinanten van posttransplantatie gewichtsveranderingen (i.e., de dosering van steroïden, leeftijd, geslacht, pretransplantatie body mass index (BMI) en dialyse modaliteit, het optreden en de behandeling van rejectie(s) en de nierfunctie na transplantatie) en de waargenomen gewichtsverandering in kaart gebracht. Het gewicht nam af in de eerste maand na transplantatie. Daarna vond er een geleidelijke gewichtstoename plaats. De gemiddelde toename in het eerste jaar na transplantatie bedroeg bijna 4 kg. Na vijf jaar was de gemiddelde gewichtstoename ruim 6 kg (ongeveer 10%). Het gewichtsverloop in het eerste jaar na transplantatie was niet afhankelijk van de onderhouds- of cumulatieve dosering steroïden, leeftijd, geslacht, het optreden van rejectie en nierfunctie. De gewichtstoename in deze periode was echter wél afhankelijk van de pretransplantatie BMI (hoe lager de BMI, hoe groter de gewichtstoename) en dialysemodaliteit (een significant grotere toename bij HD dan bij PD). Op de langere termijn bleek de

cumulatieve dosering steroïden een significant effect te hebben op de gewichtstoename: hoe hoger de cumulatieve dosering steroïden, hoe hoger de gewichtstoename.
Bij NTx-patiënten die op het moment van transplantatie ernstig ondervoed zijn (een toestand die gekarakteriseerd wordt door depletie van zowel vetmassa als vetvrije massa), is een toename van het gewicht niet noodzakelijkerwijs een negatief gegeven, omdat de gewichtstoename kan wijzen op een verbetering van hun voedingstoestand. De toenemende prevalentie van overgewicht en obesitas bij patiënten met een terminale nierinsufficiëntie die een niertransplantatie ondergaan, baart echter grote zorgen, omdat ook deze patiënten 'at risk' zijn voor een verdere gewichtstoename na de transplantatie. Excessieve gewichtstoename - en met name een significante toename van de abdominale vetmassa - heeft ongunstige effecten op het cardiovasculaire risicoprofiel (i.e., hyperlipidemie, hypertensie, insulineresistentie, posttransplantatie diabetes mellitus en het metabool syndroom) van NTx-patiënten en draagt bij aan de hoge cardiovasculaire morbiditeit en mortaliteit in deze populatie. Ook wordt de ontwikkeling van obesitas na een niertransplantatie in verband gebracht met een verminderde transplantaat- en patiëntoverleving.

Voordat onderzoek werd verricht naar de veranderingen in lichaamssamenstelling na niertransplantatie, werden in **hoofdstuk 3** eerst verschillende technieken die gebruikt kunnen worden om de lichaamssamenstelling te bepalen, onderzocht en vergeleken in NTx-patiënten.
Er zijn diverse methodieken om de lichaamssamenstelling te meten, zoals bijvoorbeeld isotoop-dilutietechnieken, anthropometrie, dual energy x-ray absorptiometry (DEXA) en multifrequente bioimpedantie analyse (MF-BIA). MF-BIA is een relatief nieuwe methode die in de dagelijkse praktijk makkelijk toepasbaar is. Met MF-BIA wordt de weerstand in het lichaam (impedantie) ten opzichte van een wisselstroom bij meerdere frequenties bepaald. Vanuit de gemeten impedantie bij wisselende frequenties kan het volume van de verschillende lichaamscompartimenten (totaal lichaamswater en extracellulair water) worden bepaald. Bij de MF-BIA methode wordt de vetvrije massa afgeleid uit het intra- en extracellulaire watervolume en wordt de vetmassa berekend door het totale lichaamsgewicht te verminderen met de vetvrije massa. Er werd bestudeerd of MF-BIA bruikbaar is om de lichaamssamenstelling van NTx-patiënten te meten. Hiertoe werd MF-BIA eerst vergeleken met de isotoop-dilutiemethode, de gouden standaard voor het meten van het totale en extracellulaire watervolume bij gezonde personen. Voor het meten van de vet- en vetvrije massa werd MF-BIA vergeleken met DEXA en anthropometrie. MF-BIA bleek een geschikte methode om de totale hoeveelheid lichaamswater bij NTx-patiënten te meten. Er werden echter relatief grote afwijkingen gevonden in het extracellulaire watervolume zoals

respectievelijk gemeten middels MF-BIA en de isotoop-dilutiemethode. Ook de betrouwbaarheid van MF-BIA om de vet- en vetvrije massa bij NTx-patiënten te meten, is twijfelachtig gebleken.

In de prospectieve studie zoals beschreven in **hoofdstuk 4**, zijn de veranderingen in lichaamssamenstelling in de eerste zes maanden na niertransplantatie onderzocht in een groep transplantatiepatiënten waarbij geen ernstige co-morbiditeit, complicaties of acute rejectie(s) optraden. De immunosuppressieve therapie van de patiënten bestond uit prednisolone (10 mg/dag), tacrolimus en mycofenolaat mofetil (MMF). De gewichtstoename bleek met name te wijten aan een toename van de vetmassa. De vetmassa, gemeten met behulp van DEXA, nam significant toe (gemiddeld 3.2 kg), terwijl slechts een kleine, niet-significante toename van de vetvrije massa (gemiddeld 0.8 kg) werd waargenomen. De toename van de vetmassa bleek het meest uitgesproken in de romp. In de cross-sectionele studie in **hoofdstuk 6** is de lichaamssamenstelling middels DEXA gemeten bij patiënten die ongeveer 9 jaar eerder een niertransplantatie hadden ondergaan. Het gemiddelde percentage lichaamsvet in deze populatie bleek hoog en bedroeg ongeveer 24% bij de mannen en 38% bij de vrouwen. Het ideale vetpercentage voor volwassenen van 30 jaar of ouder ligt voor mannen tussen de 15 en 20% en voor vrouwen tussen de 20 en 25%.

Potentiële factoren die een rol spelen bij de veranderingen in lichaams-samenstelling na niertransplantatie zijn het gebruik van immunosuppressieve medicatie, met name corticosteroïden, (veranderingen in) het voedingspatroon na transplantatie en fysieke inactiviteit. In **hoofdstuk 6** is de relatie tussen deze factoren en de lichaamssamenstelling onderzocht in een cross-sectioneel design bij NTx-patiënten die ten tijde van de studie ongeveer 9 jaar eerder getransplanteerd waren.
Er werden geen verschillen in vetmassa, vetvrije massa of de vetverdeling over het lichaam waargenomen tussen NTx-patiënten met een onderhoudsdosering steroïden van 0 mg, 5 mg of 10 mg. De patiënten in de 0-mg groep gebruikten gemiddeld ongeveer 7 jaar géén steroïden meer. Ook bleek er geen relatie te bestaan tussen de lichaamssamenstelling en de cumulatieve dosering steroïden. Zoals hierboven reeds vermeld, was het gemiddelde percentage lichaamsvet in de bestudeerde populatie relatief hoog. Bovendien was de middel-heup-ratio, een indicator voor abdominale vetverdeling, in 12% van de mannelijke patiënten en in 66% van de vrouwelijk patiënten dusdanig hoog (i.e., >1.00 bij mannen en >0.80 bij vrouwen) dat het risico voor metabole afwijkingen, hypertensie, diabetes mellitus en cardiovasculaire aandoeningen sterk toegenomen was. De resultaten van deze studie suggereren dat het

stoppen van steroïden in de latere posttransplantatie periode relatief weinig effect heeft op de lichaamssamenstelling van NTx-patiënten.
In de prospectieve, gerandomiseerde studie in **hoofdstuk 5** werden NTx-patiënten drie maanden na transplantatie toegewezen aan de groep waarin de behandeling met steroïden (10 mg/dag) werd gecontinueerd óf aan de groep waarin deze behandeling vanaf dat moment werd gestopt. In de drie maanden die volgden op de randomisatie, werd een trend waargenomen voor een grotere toename van de vetmassa in patiënten waarin de steroïd-therapie werd gecontinueerd. De verandering in vetvrije massa bleek niet verschillend tussen de groepen. In deze laatste studie werd een relatief gering aantal patiënten geïncludeerd. Bovendien was de follow-up periode kort. Het lijkt echter wel waarschijnlijk dat de effecten van steroïden op de lichaamssamenstelling het grootste zullen zijn in de vroege posttransplantatie periode, wanneer de dosering van de steroïden relatief hoog is. Het blijft onduidelijk of en in welke mate de veranderingen in lichaamsgewicht en lichaamssamenstelling na niertransplantatie toe te schrijven zijn aan de immunosuppressieve behandeling met corticosteroïden. Om deze vraag te kunnen beantwoorden is verder prospectief en gerandomiseerd onderzoek met een lange follow-up periode nodig.
Ook werd er geen relatie aangetoond tussen de inname van voedingsstoffen en de lichaamssamenstelling en lichaamsvetverdeling van NTx-patiënten. Algemeen wordt aangenomen dat de voedingsinname na transplantatie toeneemt. Dit als gevolg van een toename van het gevoel van welzijn, het wegvallen van dieetbeperkingen en een toename van de eetlust. Een toename van de energieinname via de voeding zonder dat het energieverbruik toeneemt, zal leiden tot een toename van het lichaamsgewicht. In **hoofdstuk 6** bleek dat de gemiddelde dagelijkse energie inname van NTx-patiënten iets lager was dan die van leeftijd-gematchte, gezonde volwassen Nederlanders. De inname van voedingsstoffen voldeed aan de Nederlandse Richtlijnen Goede Voeding, waarin een macronutriëntensamenstelling van 30-35 energieprocenten vet, 10-15 energieprocenten eiwit en 50-55 energieprocenten koolhydraten werd aanbevolen.
Het fysieke activiteitenniveau van de NTx-patiënten was echter relatief laag. Fysieke activiteit leek de belangrijkste factor die van invloed is op de lichaamssamenstelling van NTx-patiënten. Er werd een omgekeerde relatie waargenomen tussen de mate van fysieke activiteit en de vetmassa in het lichaam: patiënten die weinig bewogen hadden de grootste hoeveelheid lichaamsvet. Verder werd er een positieve relatie tussen de mate van fysieke activiteit en het percentage vetvrije massa waargenomen. Fysieke inactiviteit is een belangrijke risicofactor voor het ontwikkelen van het metabool syndroom. Dit syndroom kenmerkt zich door een combinatie van met elkaar samenhangende metabole risicofactoren zoals dyslipidemie (i.e., hoog plasma

triglyceriden en LDL-cholesterol, laag HDL-cholesterol), hypertensie, hyperinsulinemie, glucose intolerantie, stoornissen in de bloedstolling en abdominale obesitas. Patiënten die lijden aan het metabool syndroom hebben een verhoogd risico op het ontstaan van hart- en vaatziekten en type 2 diabetes mellitus. Bij NTx-patiënten wordt het metabool syndroom bovendien geassocieerd met een verminderde functie van de transplantaatnier.

Fysieke inactiviteit bleek ook een belangrijke determinant te zijn van de verminderde inspanningscapaciteit van NTx-patiënten **(hoofstuk 7)**. De inspanningscapaciteit en spierkracht van NTx-patiënten waren significant verlaagd (ongeveer 30%) ten opzichte van inactieve, gezonde personen en waren vergelijkbaar met die van HD-patiënten, die als gevolg van hun nierziekte en de intensieve dialysebehandelingen vaak een zeer laag fysiek activiteitenniveau hebben. De meeste transplantatiepatiënten blijven echter ook na een geslaagde niertransplantatie inactief. Bij bijna 50% van de NTx-patiënten bleek de VO_2peak gemeten tijdens een maximale inspanningstest kleiner dan 20 ml/min/kg lichaamsgewicht te zijn. Deze waarden worden geassocieerd met ernstige functionele beperkingen. De inspanningscapaciteit van de NTx-patiënten bleek zó laag te zijn dat velen beperkt zijn in het dagelijks functioneren en als gevolg hiervan een zittend bestaan leiden. Dit verhoogt het risico voor cardiovasculaire complicaties en vermindert de kwaliteit van leven. Bovendien kan fysieke inactiviteit leiden tot spierzwakte, een andere belangrijke determinant van de verminderde inspanningscapaciteit bij NTx-patiënten. Fysieke training en het bewerkstelligen van een hoger fysiek activiteitenniveau kan de vicieuze cirkel waarin veel NTx-patiënten zich bevinden, mogelijk doorbreken.

In **hoofdstuk 8** zijn daarom de effecten van fysieke training op de lichaamssamenstelling, inspanningscapaciteit, spierkracht en gezondheidsgerelateerde kwaliteit van leven onderzocht en vergeleken in NTx-patiënten, HD-patiënten en gezonde, inactieve controlepersonen. Het intensieve, gestandaardiseerde, 12 weken durende trainingsprogramma bestond uit een combinatie van duur- en krachttraining. Voor iedere deelnemer werd -gebaseerd op de resultaten van de maximale inspanningstesten die op baseline werden verricht- een individueel programma ontwikkeld. De nierpatiënten en controlepersonen volgden twee trainingssessies per week. Iedere sessie duurde twee uur en bestond uit fietsen, lopen op de loopband, krachtoefeningen op fitnesstoestellen, en alternerend zwemmen en oefeningen of spel in de gymzaal. Training vond plaats in groepen waarin zowel nierpatiënten als controlepersonen participeerden.
Het trainingsprogramma bracht geen significante veranderingen teweeg in het lichaamsgewicht en de lichaamssamenstelling van NTx- en HD-patiënten. Bij

de controlepersonen daarentegen - met name bij de mannen - nam het gewicht toe als gevolg van een toename van de vetvrije massa. Bij de NTx-patiënten leek het gebruik van corticosteroïden de effecten van training op de vet- en vetvrije massa niet te beïnvloeden. Het gebruikte trainingsprogramma bleek dus vooralsnog geen effect te hebben op het gewicht en de vetmassa van NTx-patiënten. Waarschijnlijk is het programma niet voldoende intensief en/of te kort geweest om dit te kunnen bewerkstelligen. Verder onderzoek is nodig om de beste strategie te ontrafelen om de gewichtstoename en toename van de hoeveelheid lichaamsvet na niertransplantatie te beheersen. Veel lichaamsbeweging lijkt met name ook belangrijk te zijn om een excessieve toename van het gewicht te voorkómen. Daarom is het van belang dat fysieke training en het bewerkstelligen van veranderingen in leefstijl bij patiënten met nieraandoeningen reeds in een zo vroeg mogelijke fase van chronisch nierfalen, i.e., in de predialyse- en dialysefase, plaatsvindt.
Het trainingsprogramma had wel zeer gunstige effecten op de inspanningscapaciteit en spierkracht van NTx- en HD-patiënten. De inspanningscapaciteit en de kracht namen gemiddeld met ongeveer 20-25% toe. Bovendien trad er een significante verbetering op in de gezondheidsgerelateerde kwaliteit van leven van de NTx- en HD-patiënten. Het gebruik van lage doseringen corticosteroïden bleek de respons op training bij NTx-patiënten niet te beïnvloeden. Overigens bleek de functionele respons op het gestandaardiseerde trainingsprogramma (i.e., de respons voor wat betreft inspanningscapaciteit en spierkracht) niet te verschillen tussen NTx-patiënten, HD-patiënten en gezonde controlepersonen. Nierpatiënten kunnen derhalve goed getraind worden. De inspanningscapaciteit en spierkracht van de NTx- en HD-patiënten waren na de trainingsinterventie wel nog steeds lager dan die van inactieve controlepersonen. Het was echter ook geen eindpunt van de studie om hetzelfde niveau als gezonde controlepersonen te bereiken. Hiervoor was de duur van het programma te kort. Langer durende interventies zullen moeten uitwijzen of training de inspanningcapaciteit en kracht van nierpatiënten nog verder kan doen toenemen en of het niveau van gezonde personen kan worden bereikt.

Inspanningstraining heeft de potentie om de gezondheidstoestand van dialysepatiënten te verbeteren door een toename van de inspanningscapaciteit, spierkracht en gezondheidsgerelateerde kwaliteit van leven. Bij NTx-patiënten kunnen de gunstige effecten van training mogelijk ook de ontwikkeling van nieuwe medische problemen zoals obesitas, afwijkingen in het vetspectrum, posttransplantatie diabetes mellitus en cardiovasculaire aandoeningen, voorkomen. Training kan de negatieve spiraal van deconditionering bij HD- en NTx-patiënten doorbreken. Het is dan ook van groot belang dat er meer aandacht besteed wordt aan fysieke training en het

bewerkstelligen van een actievere leefstijl bij deze patiëntenpopulaties. Training dient daarom een structureel onderdeel te worden van de routinebehandeling van zowel dialyse- als transplantatiepatiënten. Op dit moment wordt er te weinig aandacht besteed aan fysieke training in de reguliere zorg voor de nierpatiënt.

De kosten voor dialysebehandeling bedragen ongeveer 50.000 - 60.000 euro per patiënt per jaar. Een niertransplantatie kost ongeveer 60.000 euro in het eerste jaar, terwijl de kosten van de levenslange nefrologische medische zorg daarna ongeveer 10.000 euro per patiënt per jaar bedragen. De geschatte kosten van trainingsprogramma's voor nierpatiënten (ongeveer 2000 euro per patiënt in het eerste jaar en daarna ongeveer 750 euro per jaar) zijn verwaarloosbaar vergeleken bij de kosten voor de gezondheidszorg. De potentiële opbrengst van fysieke training kan mogelijk leiden tot een aanzienlijke besparing van kosten op de langere termijn. Alhoewel de korte-termijn effecten van training zijn aangetoond, wordt deelname aan een trainingsprogramma niet door de zorgverzekeraars vergoed. Dit vormt een barrière voor de implementatie van trainingsprogramma's, omdat de meeste patiënten niet over de financiële middelen beschikken om dergelijke programma's zelf te bekostigen. De lange-termijn effecten en de kosten-effectiviteit van inspanningstraining zullen vastgesteld moeten worden om de zorgverzekeraars ervan te overtuigen dat inspanningstraining efficiënt is en vergoed dient te worden.

Dankwoord

Dankwoord

Na vele jaren met veel plezier aan dit proefschrift te hebben gewerkt, is het dan eindelijk af! Zonder de hulp en inzet van velen was dit niet gelukt. Ik wil dan ook iedereen die betrokken is geweest bij de totstandkoming van het proefschrift heel hartelijk bedanken, in het bijzonder degenen hieronder genoemd.

Allereerst een bijzonder woord van dank aan alle nierpatiënten die aan de verschillende onderzoeken hebben deelgenomen. Zonder jullie medewerking was het niet mogelijk geweest om het onderzoek uit te voeren! Ik heb grote waardering voor degenen die aan de intensieve trainingsstudie hebben deelgenomen. Jullie inzet, motivatie en enthousiasme was indrukwekkend. Het was geweldig om te zien hoeveel plezier jullie samen beleefden tijdens de trainingen. Ik heb bewondering voor de manier waarop jullie elkaar wisten te stimuleren, met name ook op die dagen dat het voor sommigen moeilijk was en allemaal minder goed lukte. Ik hoop dat jullie veel profijt van deze studie hebben gehad en dat het jullie allen goed gaat en zal blijven gaan! Ook de gezonde controlepersonen, waaronder vele partners van de patiënten, wil ik danken voor hun bereidwilligheid om aan de trainingsstudie mee te werken.

Mijn promotores Prof. dr. J.P. van Hooff, Prof. dr. ir. A.M.W.J. Schols en Prof. dr. K.M.L. Leunissen wil ik bedanken voor de mogelijkheid die zij mij hebben geboden om het in dit proefschrift beschreven onderzoek uit te voeren. Professor van Hooff, bedankt voor het vertrouwen in mij en mijn werk, voor de vrijheid die ik heb gekregen om zelfstandig te werken aan het onderzoek, voor de prettige samenwerking en begeleiding en voor de kritische beoordeling van alle manuscripten. Professor Schols, beste Annemie, jij was een onmisbare schakel in mijn promotieonderzoek. De samenwerking met het Astmacentrum Hornerheide kwam via jou tot stand. Jouw enthousiasme en wetenschappelijke kennis en interesse op het gebied van voeding en metabolisme bij chronische ziekten zijn ongekend. Bedankt voor je altijd kritische blik op de onderzoeksgegevens, voor alle waardevolle discussies die we hierover hebben gevoerd en voor de suggesties voor het verder uitwerken van nieuwe onderzoeksvragen. Bedankt voor de fijne samenwerking en voor alle steun en toewijding. Professor Leunissen, ook u bedankt voor uw bijdrage aan de totstandkoming van dit proefschrift.

Mijn copromotor Dr. J.P. Kooman, wil ik bedanken voor de meer dagelijkse begeleiding van het onderzoek. Beste Jeroen, jouw enthousiasme voor wetenschappelijk onderzoek en de snelheid waarmee jij onderzoeksresultaten op een rij weet te zetten, zijn indrukwekkend. Bedankt voor je geduld, voor de

prettige samenwerking en begeleiding en voor álles wat jij voor mijn promotieonderzoek hebt gedaan! Ik hoop dat we in de toekomst - in nauwe samenwerking met Annemie - nog veel wetenschappelijk onderzoek in Maastricht kunnen opzetten.

De leden van de beoordelingscommissie, Prof. dr. Wouters (voorzitter), Prof. dr. Floege, Prof. dr. Kuipers, Dr. Painter en Prof. dr. Westerterp, wil ik bedanken voor hun bereidwilligheid om het manuscript te beoordelen. Prof. dr. Floege and Dr. Painter, thank you for your willingness to be one of the reviewers of the manuscript. Dr. Painter, dear Trish, your research group has performed a lot of research in the field of physical performance and the effects of training in dialysis and renal transplant patients. I am very honored that you are willing to come to Maastricht to attend the degree ceremony!

De trainingsstudie beschreven in dit proefschrift was niet mogelijk geweest zonder het Astmacentrum Hornerheide in Horn (tegenwoordig Centrum voor Integrale Revalidatie Orgaanfalen, CIRO Horn). Rob Mostert en Paul Janssen, bedankt voor alle mogelijkheden die jullie hebben gecreëerd om de trainingsstudie voor niertransplantatie- en hemodialysepatiënten uit te kunnen voeren. Beste Paul, jouw bereidwilligheid, enthousiasme en betrokkenheid bij het project waren groots. Bedankt voor alles wat je gedaan hebt om dit project zó succesvol te laten verlopen!

Het team van bewegingsagogen van de afdeling Bewegingsagogie in Hornerheide verdient een speciaal woord van dank. Beste Marco, Tom, Jerôme, Anne, Leon en Remco, jullie gedrevenheid, enthousiasme en de manier waarop jullie patiënten wisten te motiveren tijdens de vele kracht- en inspanningtesten en tijdens de trainingen, was grandioos! Zelfs als het voor sommige patiënten eens een dag niet wilde lukken, wisten jullie er toch altijd voor te zorgen dat diegenen met een voldaan gevoel naar huis gingen. Ook hebben jullie mij enorm geholpen met het maken van de vaak zo complexe planningen van alle fiets- en krachttesten, spierbiopten en de metingen van het rustmetabolisme en bij het zoeken naar gezonde vrijwilligers voor de trainingsstudie. Ouders, vrienden en (partners van) collega's, ze werden allemaal ingeschakeld. Bedankt voor jullie geweldige inzet, voor de fijne samenwerking en voor alle gezelligheid in en om het honk van de Bewegingsagogie in Hornerheide! Het was een fantastische tijd die ik nooit zal vergeten.

Bijzonder veel dank gaat ook uit naar Joan Does. Beste Joan, wat had ik zonder jou moeten beginnen? Ondanks jouw drukke klinische werkzaamheden stond jij áltijd voor mij klaar! Jij wist toch altijd tijd vrij te maken voor het

trainingsonderzoek bij de nierpatiënten, voor het nemen van spierbiopten, voor de medische begeleiding van de fietstesten en voor het als arts aanwezig zijn bij de trainingen die veelal in de avonduren plaatsvonden. Zonder jouw inzet was de trainingsstudie nooit zo'n succes geworden!

Frits Franssen, beste Frits, ik wil je heel hartelijk bedanken voor al die keren dat jij bijgesprongen bent om spierbiopten te nemen en fietstesten te begeleiden op momenten dat er in een kort tijdsbestek vele patiënten getest moesten worden. Ik wens je veel succes met je verdere opleiding tot longarts en met het afronden van jouw promotieonderzoek!

Annelies, Gonnie, Monique en Peggy van het laboratorium in Hornerheide, jullie hebben me geweldig geholpen bij het verwerken van de bloedmonsters op momenten dat het erg druk was en jullie hebben vele bepalingen in het kader van mijn studie verricht. Marianne en Kitty van de longfunctie in Hornerheide, ook jullie stonden altijd voor mij klaar. Bedankt voor al jullie hulp, belangstelling en gezelligheid!

Beste Sjef, u was een zéér belangrijke spil in het vervoer van de patiënten vanuit heel Limburg naar Hornerheide. Veel patiënten beschikten niet over eigen vervoer of waren niet in staat om na een intensieve training zelf naar huis te rijden. De 'vervoerslogistiek' was echt een crime! We hebben heel wat 'Sightseeing Limburg' gedaan, vaak zelfs meerdere keren op één dag. Bijna altijd wist u tijd vrij te maken voor 'mijn' patiënten en als dat écht niet lukte werden zelfs familieleden ingeschakeld om mij uit de brand te helpen. Zonder uw belangeloze inzet hadden veel patiënten niet aan de trainingsstudie deel kunnen nemen! Daarom ook namens hen nogmaals héél hartelijk bedankt!

Alle nefrologen in de regio die zich ingezet hebben om patiënten in de trainingsstudie te includeren wil ik hartelijk bedanken. Dr. J. Wirtz en Drs. W. Grave (Laurentius Ziekenhuis Roermond), Drs. F. de Heer (Maasland Ziekenhuis Sittard), Drs. V. Verstappen en Dr. A. Luik (VieCuri Venlo) en Dr. P. Douwes-Draaijer en Dr. C. Konings (Catharina Ziekenhuis Eindhoven), bedankt voor de prettige samenwerking. Ook de dialyseverpleegkundigen in het azM en in de perifere dialysecentra, in het bijzonder Suzan Jeuken, Anne Delissen, Angeline Cuypers en Marieke Emmen, bedankt voor jullie inzet, voor jullie hulp bij het includeren van patiënten en voor het regelen van diverse praktische zaken zoals de afname van bloedmonsters en het verzamelen van medische gegevens van patiënten.

Lia, Florence en Sandra van de afdeling Nucleaire Geneeskunde in het azM wil ik graag bedanken voor het maken van de vele DEXA scans voor het project TA6.

Kimberley Ward, Harry Gosker en Jamie Macdonald wil ik bedanken voor het analyseren van het verzamelde spierweefsel en voor hun hulp bij het interpreteren van de spierbioptdata. Dear Jamie, thank you for doing the IGF-analyses in the serum and muscle biopsy samples and for your valuable help in interpreting the IGF-data. I wish you a lot of success with the tail end of your PhD project!

Fred Nieman, beste Fred, heel wat uren ben jij de afgelopen jaren bezig geweest om uit te zoeken welke - vaak lastige - statistische analyses het beste op mijn onderzoeksgegevens konden worden toegepast. Als je dat eenmaal uitgevogeld had, deed je me hier uitgebreid en zeer gedetailleerd verslag van. Ik bewonder jouw passie voor de methodologie en de manier waarop jij telkens vol enthousiasme en met veel geduld aan mij probeerde uit te leggen waarom bepaalde analyses wél en andere weer zeker niet mochten worden toegepast en hóe de analyses moesten worden uitgevoerd. Vergeef me dat ik de naslagwerken uit jouw boekenkast, die een en ander verder zouden kunnen verduidelijken, niet altijd tot in detail heb bestudeerd. Voor problemen en hulp bij de uitvoering van de analyses en vragen over de interpretatie van de vaak complexe output files, kon ik altijd bij jou terecht. Bedankt voor alles wat jij mij hebt geleerd op het gebied van statistiek! De complimenten, die ik meer dan eens kreeg van de reviewers voor de gedegen en uitgebreide statistiek, zijn dan ook vooral aan jou gericht.

Ook de vroegere en huidige collega's van de werkgroep Nefrologie in het azM wil ik bedanken. Zonder een goede basis kun je niet werken. Maarten Christiaans, Elly van Duijnhoven, Mariëlle Gelens, Frank van der Sande, Mark Hermans, Jos van de Kerkhof, Martine Verhoeven, Christine Verhoeven, Charles Beerenhout, Stijn Konings, Hans Boots en Jos Barendregt, bedankt voor de fijne samenwerking en jullie hulp bij de 'medisch-praktische' uitvoering van de verschillende studies. Etiënne Maas, Anke Hendriks, Lilian Sanders, Monique Mullens, John Dackus en Philip Ulrichts, ook jullie heel hartelijk bedankt voor de prettige samenwerking, gezelligheid en het vaak luisterende oor.

Evelien Pijpers en Riquette Hulsewé, oud-kamergenoten. Wat hebben we veel gelachen en veel plezier gehad! Ik mis deze gezellige momenten en de wetenschappelijke discussies onder het genot van een kopje thee. Maar er zijn ook heel wat traantjes op onze kamer gelaten. Het was fijn om op deze

moeilijke momenten steun en een luisterend oor bij elkaar te vinden en er voor elkaar te zijn! Evelien, ik wens je de komende tijd veel succes met je onderzoek en het schrijven van je proefschrift. Riquette, heel veel succes verder op de Intensive Care afdeling en veel geluk thuis, samen met Karel en jullie vier kinderen.

Beeldend kunstenaar Sjer Jacobs wil ik bedanken voor de omslag van het proefschrift. Beste Sjer, toen ik eind vorig jaar in Tegelen in de galerie langskwam met de vraag of jij een kunstwerk zou kunnen maken voor de omslag van mijn proefschrift, was jij onmiddellijk enthousiast. Terwijl ik je iets meer vertelde over mijn onderzoek naar de effecten van training bij dialyse- en niertransplantatiepatiënten, was jij al druk in de weer met het maken van een aantal eerste schetsen. Mijn keuze viel op je ontwerp 'In beweging'. In één beeld heb je de verandering van inactiviteit naar beweging zichtbaar gemaakt. Het is juist deze verandering die ik zo graag bij zoveel mogelijk nierpatiënten zou willen zien. Ik ben je zeer erkentelijk voor het schitterende resultaat! Het zal mij iedere dag opnieuw herinneren aan de geweldige tijd die ik met de nierpatiënten tijdens de trainingsstudie heb beleefd.

Tiny Wouters, beste Tiny, heel hartelijk bedankt voor alle tijd en energie die jij in de lay-out van mijn proefschrift hebt gestoken. Jouw expertise, geduld en oog voor detail hebben geleid tot een fantastisch resultaat!

Lieve oma Flos, lieve To, wat ben jij altijd trots geweest op je petekind en oudste kleindochter! Bedankt voor je oprechte steun, belangstelling en interesse in mijn werk. Eindelijk is het proefschrift nu klaar en staat de promotiedatum vast! Het ging voor jou allemaal niet snel genoeg, omdat je bang was dat je de promotie niet meer mee zou kunnen maken. Maar denk eraan wat we samen hebben afgesproken! Ook al is het nu - na je operatie - een moeilijke tijd voor je, het zal je best lukken om er op deze voor ons allebei zo bijzondere dag bij te zijn!

Emile en Janneke, Frédérique en Martijn en Richard en Nicole, wat is het heerlijk als het als broers en zussen en hun aanhang onder elkaar zo goed klikt! Bedankt allemaal voor jullie belangstelling, steun, luisterend oor en bemoedigende woorden op momenten dat ik het even allemaal niet meer zag zitten en voor jullie hulp bij de voorbereidingen van mijn promotie. Lieve Emile en Fré, ik ben er zeer trots op dat jullie bij mijn promotie paranimf zijn. Betere paranimfen had ik mij niet kunnen wensen. Jullie hebben mij enorm gesteund en samen heel veel werk uit handen genomen!

Lieve Idy en Har, jullie hebben mij, Emile, Frédérique en Richard op een geweldige manier in het leven gezet! Jullie waren en zijn er altijd voor ons! Bedankt voor jullie onvoorwaardelijke steun! De geweldige ‘Sjer’ die op de omslag is afgedrukt, zal als herinnering aan mijn promotieonderzoek een hele bijzondere plek krijgen in ons huis in Klimmen!

Lieve Niki, jij bent mijn steun en toeverlaat, mijn rots in de branding! Als geen ander weet jij hoe belangrijk een goede relatie en rust op het thuisfront zijn in moeilijke tijden. Jouw geduld was grenzeloos. Bedankt voor je intense vertrouwen in mij. Zonder jou was het niet gelukt!

Abbreviations

Abbreviations

ANCOVA	analysis of covariance
ANOVA	analysis of variance
BF	body fat
BID	bidaily
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BP	bodily pain
BPr	blood pressure
BW	body weight
CAN	chronic allograft nephropathy
CAPD	continuous ambulatory peritoneal dialysis
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
CV	coefficient of variation
DEXA	dual energy x-ray absorptiometry
ECW	extra-cellular water
ESRD	end-stage renal disease
FFM	fat-free mass
FM	fat mass
GH	general health
GOX	glucose oxidation rate
Hb	hemoglobin
HD	hemodialysis
HDL	high density lipoprotein
HR	heart rate
HRpeak	peak heart rate
HRRpeak	peak heart rate reserve
IBW	ideal body weight
ICC	intraclass correlation coefficient
ICW	intracellular water
K-DOQI	Kidney Disease Outcomes Quality Initiative
LAI	leisure activity index
LBM	lean body mass
LDL	low density lipoprotein
LM	lean mass
LOX	lipid oxidation rate

MAC	mid-upper arm circumference
MCS	mental component scale
MF-BIA	multi-frequency bio-electrical impedance analysis
MH	mental health
MIA	malnutrition–inflammation–atherosclerosis
MMA	mid-arm muscle area
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
N_{urine}	urinary nitrogen excretion
OAI	occupational activity index
PAL	physical activity level
PCKD	polycystic kidney disease
PCS	physical component scale
PF	physical functioning
Pmax	maximal strength
POX	protein oxidation rate
PTH	parathyroid hormone
QoL	quality of life
RE	role functioning - emotional
REE	resting energy expenditure
RER	respiratory exchange ratio
RP	role functioning - physical
RTx	renal transplant
SAI	sport activity index
SD	standard deviation
SDD	smallest detectable difference
SF	social functioning
SF-36	medical outcomes study short-form-36
ST+	steroid-based immunosuppression
ST-	steroid-free immunosuppression
TAI	total activity index
TBW	total body water
Tx	transplantation
VCO_2	carbon dioxide production
VLDL	very-low density lipoprotein
VO_2	oxygen uptake
VO_2peak	peak oxygen uptake
VT	vitality
Wpeak	peak work rate / peak work load

Publications

Publications

van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Kreel BK, Heidendal GA, van Hooff JP. Body composition in renal transplant patients: bio-impedance analysis compared to isotope dilution, dual energy x-ray absorptiometry, and anthropometry. J Am Soc Nephrol. 1999; 10(5): 1067-1079.

van Houwelingen AC, van den Ham EC, Hornstra G. The female docosa-hexaenoic acid status related to the number of completed pregnancies. Lipids. 1999; 34(Suppl):S229.

van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. Relation between steroid dose, body composition and physical activity in renal transplant patients. Transplantation. 2000; 69(8):1591-1598.

van den Ham EC, Kooman JP, Christiaans MH, Leunissen KM, van Hooff JP. Posttransplantation weight gain is predominantly due to an increase in body fat mass. Transplantation. 2000; 70(1):241-242.

Kooman JP, Cox-Reijven PL, van der Sande FM, van den Ham EC, Leunissen KM. Assessment of body composition in ESRF. Kidney Int. 2001; 59(1): 383-384.

van den Ham EC, van Houwelingen AC, Hornstra G. Evaluation of the relation between n-3 and n-6 fatty acid status and parity in nonpregnant women from the Netherlands. Am J Clin Nutr. 2001; 73(3):622-627.

van den Ham EC, Kooman JP, van Hooff JP. Nutritional considerations in renal transplant patients. Blood Purif. 2002; 20(2):139-144.

Boots JM, van den Ham EC, Christiaans MH, van Hooff JP. Risk of adrenal insufficiency with steroid maintenance therapy in renal trans-plantation.Transplant Proc. 2002; 34(5):1696-1697.

van den Ham EC, Kooman JP, Christiaans MH, van Hooff JP. The influence of early steroid withdrawal on body composition and bone mineral density in renal transplantation patients. Transpl Int. 2003; 16(2):82-87.

van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Hooff JP. Weight changes after renal transplantation: a comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immuno-suppressive therapy. Transpl Int. 2003; 16(5):300-306.

van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Franssen FM, Akkermans MA, Janssen PP, van Hooff JP. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. Am J Transplant. 2005; 5(8):1957-1965.

van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Akkermans MA, Janssen PP, Gosker HR, Ward KA, Macdonald JH, Christiaans MH, Leunissen KM, van Hooff JP. The functional, metabolic and anabolic response to exercise training in renal transplant and hemodialysis patients. Submitted for publication.

van den Ham EC, Kooman JP, Schols AM, Gosker HR, Ward KA, Does JD, Franssen FM, Macdonald JH, Christiaans MH, Leunissen KM, van Hooff JP. A comparative study on skeletal muscle MyHC composition, enzyme activity and the IGF-system in renal transplant patients and healthy controls. Submitted for publication.

Curriculum vitae

Curriculum vitae

Eugénie Catharina Hubertina van den Ham was born on November 27th, 1971 in Tegelen, The Netherlands. She finished high school (Gymnasium β, Sint Thomascollege, Venlo) in 1991. In the same year, she started the study Health Sciences at the University of Maastricht (major Biological Health Sciences). In August 1996, she graduated at the Department of Human Biology of the University of Maastricht on a research project on the relation between the maternal fatty acid status and the number of completed pregnancies, under the supervision of Prof. dr. G. Hornstra and Dr. A.C. van Houwelingen. During her study, she performed a facultative internship on the weight changes after renal transplantation at the Department of Internal Medicine, Division Nephrology, of the University Hospital Maastricht (supervision by Prof. dr. J.P. van Hooff and Dr. M.H.L. Christiaans). From September 1996 until May 2000, she joined this department as a research-assistant. In May 2000, she received a research grant of the Dutch Kidney Foundation for the research project 'Body composition and muscle dysfunction in renal patients: underlying mechanisms and the response to exercise training'. This project was carried out at the Department of Internal Medicine (Division Nephrology) of the University Hospital of Maastricht under supervision of Prof. dr. J.P. van Hooff, Prof. dr. ir. A.M.W.J. Schols, Prof. dr. K.M.L. Leunissen, and Dr. J.P. Kooman and resulted in the present thesis. Since April 2004, she also has joined the national project group on Integrated Care of Renal Transplantation as a quality coordinator. In this capacity, she also has been involved in the development of an integrated quality management system for renal transplantation in the Maastricht University Hospital. Currently, she works at the Department of Internal Medicine (Division Nephrology) of the University Hospital of Maastricht, both as scientific researcher and quality coordinator.