Physical Performance and Exercise Training in Patients with Chronic Kidney Disease

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in Patients with Chronic Kidney Disease

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Observational and Interventional Studies

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Abstract

The overall aim of this thesis was to investigate the importance of physical performance and regular exercise training in patients with CKD.

Methods

Survival was analysed retrospectively in relation to physical performance prior to start in chronic dialysis treatment (Study I). In RENEXC, a randomized controlled clinical trial, patients with non-dialysis dependent CKD were randomized to 90 minutes strength- (SG) or balance- (BG), both combined with 60 minutes endurance exercise training for 150 minutes/week for 12 months, monitored by Borg's Rating of Perceived Exertion. The primary outcomes were measures of physical performance, the secondary outcomes were measures of kidney function. (Studies II, III and IV).

Results

In study I, handgrip strength (HGS) (p_{right}=0.006, p_{left}=0.004), heel rises (p_{right}=0.01, p_{left}=0.004), functional reach (p=0.01), age (p<0.001) and comorbidity (p=0.03) were associated with survival. A 50% decrease in HGS left corresponded to an almost three fold increase in mortality after adjustment for age, sex and comorbidity. In a RENEXC baseline analysis, comprising 101 patients showed impaired physical performance. Deterioration in 6 minute walk test (6-MWT, p=0.04), quadriceps strength (p_{left}=0.04), functional reach (balance, p=0.02) and Moberg's picking up test (fine motor skills) in the left hand with open eyes (p=0.01) corresponded to a decline in mGFR. A decline of 10 ml/min/1.73m^2 corresponded with a 35 meters shorter walking distance and a 10% decrease in quadriceps strength left. In RENEXC, 151 patients were included (mean age: 66±14; mGFR: 22±8 ml/min/1.73m^2). Both groups improved or maintained physical performance after 4 and 12 months exercise training. Improvements after 12 months, (***=p<0.001; **=p<0.01; *=p<0.05), were found for 6-MWT (SG***; BG***), stair climbing (SG***; BG***); 30-STS (30 seconds sit to stand, SG***; BG**), heel rises (SG: right***, left***; BG: right***, left***), toe lifts (SG: right**, left**; BG: right***; left***); quadriceps strength (SG: right***, left**; BG: right**, left**); functional reach (SG**; BG**); Moberg's picking up test right (SG: open***, closed*** eyes, BG: closed* eyes) and left (SG: open**, closed* eyes; BG: open* eyes). mGFR declined by 1.8 mL/min/1.73m^2 in SG** and BG**; urine-albumin-creatinine-ratio decreased by 33% from 98 to 64 mg/mmol in SG*** and was maintained in BG.

Conclusion

Handgrip strength left seems to be a strong predictor of survival in patients on maintenance dialysis. Physical performance seems to be impaired early in the course of CKD and further decline seems to be related to a decrease in GFR. Regular exercise training improves physical performance and may have positive effects on kidney function.

Key words: Physical Performance, Exercise Training, Endurance, Strength, Balance, Fine Motor Skills Chronic Kidney Disease (CKD), Glomerular Filtration Rate (GFR)

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An all die Menschen, die diese Arbeit haben Wirklichkeit werden lassen

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This thesis is based on the following publications:

Study I Small Distal Muscles and Balance Predict Survival in End-Stage Renal Disease
Matthias Hellberg, Eva Maria Wiberg, Ole Simonsen, Peter Höglund, Naomi Clyne
Nephron Clin Pract 2014;**126**:116-123

Study II Decline in Measured Glomerular Filtration Rate is Associated with a Decrease in Endurance, Strength, Balance and Fine Motor Skills
Matthias Hellberg, Peter Höglund, Philippa Svensson, Huda Abdulahi, Naomi Clyne
Nephrology Carlton 2017;**22**:513-519

Study III Comparing Effects of 4 Months of Two Self-administered Exercise Training Programs on Physical Performance in Patients with Chronic Kidney Disease
Matthias Hellberg, Peter Höglund, Philippa Svensson, Naomi Clyne
Under revision PLOS ONE

Study IV Physical Performance, GFR and Albuminuria after 12 Months of Self-administered Exercise Training in Patients with CKD: RENEXC – a Randomized Controlled Clinical Trial
Matthias Hellberg, Peter Höglund, Philippa Svensson, Naomi Clyne
Submitted

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Abbreviations

BMI	body mass index
CKD	chronic kidney disease
DD-CKD	dialysis dependent – chronic kidney disease
NDD-CKD	non-dialysis dependent – chronic kidney disease
DEXA	dual energy x-ray absorptiometry
GFR	glomerular filtration rate
eGFR	estimated GFR
eGFR(Crea)	estimated GFR, based on plasma/serum-creatinine
eGFR(CysC)	estimated GFR, based on plasma/serum-cystatine-C
mGFR	measured GFR (iohexol clearance)
MET	metabolic equivalent of tasks or only metabolic equivalent
RCT	randomized controlled trial
SRR	Swedish Renal Registry
U-ACR	urine-albumin-creatinine-ratio
VO_{2max}	aerobic capacity, maximum
W_{max}	working or exercise capacity, maximum
6-MWT	6-minute walk test
30-STS	sit to stand test within 30 seconds
60-STS	sit to stand test within 60 seconds
STS-5	sit to stand test, the time it takes to perform 5 repetitions
STS-10	sit to stand test, the time it takes to perform 10 repetitions
RM	repetition maximum

Introduction

The kidneys play a central role in the body's homeostasis. They regulate fluid-, electrolyte- and acid-base-balance, filter waste products and have a series of endocrine functions like production of renin, erythropoietin, and activation of vitamin D. Loss of kidney function leads to an imbalance in this homeostasis. The more severe loss of kidney function, the more pronounced and life threatening may the consequences be for the individual. A number of symptoms usually appear as kidney function declines. Among the most common symptoms are fatigue, weakness, nausea, loss of appetite, loss of strength and energy, tiredness, lack of stamina, inactivity and passivity, difficulty concentrating and depression.

Kidney function

Glomerular filtration rate (GFR)

The nephron is the functional unit in the kidneys and each kidney contains about one million nephrons. The nephron consists of glomerular capillaries surrounded by Bowman's capsule, which is connected to the tubular system. About 1.2 L of blood flows through the capillaries per minute, which corresponds to 25% of the blood volume delivered by the heart per minute. About 20% of the renal plasma volume, 650 ml per minute, is filtered in the glomeruli and about 120 ml primary urine is produced per minute. This constitutes the glomerular filtration rate, which normally is about 90 to 120 ml/min in healthy subjects. The primary urine volume amounts to about 170 L per day and is concentrated in the tubular system to about 1 to 2 L of final urine per day. The glomerular filtration rate is crucial for the elimination of substances that the body wants to get rid of. This clearance function corresponds to the kidneys' glomerular filtration rate of substances, which are not affected by tubular reabsorption or secretion and not eliminated by other organs. Thus, the glomerular filtration rate (GFR) is used to evaluate kidney function. In order to be able compare measurements of GFR between individuals of different sizes, the international standard is to specify the GFR in relation to a body surface area of $1.73m^2$.

Chronic kidney disease (CKD)

According to the level of estimated GFR, defined as ml/min/1.73m^2, in patients with chronic kidney disease, 5 stages have been agreed upon internationally (table 1).[1] The decrease of kidney function has to be stable for at least three months in order to be defined as chronic kidney disease (CKD). There are a number of causes for chronic kidney disease. Hypertension and diabetes mellitus are considered to be the most frequent causes of CKD in developed countries, especially in elderly.[1] Chronic glomerulonephritis, chronic pyelonephritis and adult polycystic kidney disease are also common aetiologies for CKD.

Table 1.
CKD stages[1]

CKD –stages (GFR category)	eGFR (ml/min/1.73m^2)	Terms
1 (G1)	≥90	normal
2 (G2)	60-89	mildly decreased
3a (G3a)	45-59	mildly to moderately decreased
3b (G3b)	30-44	moderately to severely decreased
4 (G4)	15-29	severely decreased
5 (G5)	<15	kidney failure

CKD – progression, morbidity and mortality

CKD is common with a global prevalence of about 10% and is associated with high morbidity and mortality.[2-4] A 15 ml/min/1.73m^2 lower eGFR below a threshold of 45 ml/min/1.73m^2 was independently associated with increased mortality and a faster arrival at end stage renal disease.[5] The risk of reaching end stage renal disease was unrelated to eGFR levels between 75 and 105 ml/min/1.73m^2, but the hazard ratio was 4 at 60 ml/min/1.73m^2 and 29 at 45 ml/min/1.73m^2.[6] Decreased levels of eGFR and increased albuminuria are both considered to be independent risk factors for the progression of chronic kidney disease and for reaching end stage renal disease.[7] The high risk of mortality in patients with CKD is well known and mostly due to cardiovascular comorbidity or infections.[1, 8, 9] Twenty to thirty year old patients with dialysis dependent CKD (DD-CKD) showed a cardiovascular mortality similar to 80 year olds in the general population.[10]

Measured glomerular filtration rate (mGFR)

For the exact measurement of GFR, an invasive clearance method, such as iohexol clearance, is required. Iohexol is a radiological contrast substance, which is water-soluble and non-protein bound, and freely filtered through the glomeruli without tubular influence. Iohexol is used as tracer substance and given as an intravenous injection. Thus, the exact GFR can be estimated by measuring the plasma concentration and elimination rate. The measurement of iohexol clearance is part of routine follow up of patients with CKD at our department and the analyses are performed by the Department of Clinical Chemistry at Laboratory Medicine, Skåne.[11, 12] The inaccuracy, which may occur when using an estimation of GFR based on, for example, P-creatinine or P-cystatine C, especially at the lower stages of CKD, can be addressed by measuring iohexol clearance. Other tracer substances that can be used instead of iohexol are for example ^{51}Cr-EDTA or ^{131}I-iothalamate. Inulin is the classic tracer substance and renal clearance of inulin is considered to be the reference method to measure GFR, but not practical in clinical routine.

Estimated glomerular filtration rate (eGFR)

GFR can be estimated by prediction equations based on P-cystatin C and or P-creatinine and anthropometric data.[13] The mean eGFR (relative) is the estimate of the patient's relative eGFR in ml/min/1.73m^2. After estimation of eGFR$_{(CyC)}$ and eGFR$_{(Crea)}$ in ml/min/1.73m^2, the mean of both estimates is calculated as mean eGFR (relative) and used as eGFR$_{(CyC/Crea)}$.[13-16]

Cystatin C is a protease, excreted from all nuclear cells in the body and occurs in all extracellular spaces. Renal clearance is similar to iohexol or other small molecules, but after glomerular filtration cystatin C is almost completely reabsorbed and catabolized in the proximal tubules cells in the kidneys. There is no tubular secretion. The level of cystatin C is not influenced significantly by muscle mass, sex or inflammation. Thus, the concentration of P-cystatin C corresponds well to GFR. Even a moderate or an age-related decrease in GFR can be detected by measuring P-cystatin C and estimating GFR as eGFR$_{(CyC)}$.[13, 14]

Creatinine is a metabolic end product of muscle activity and metabolism and is related to muscle mass. Creatinine is eliminated by glomerular filtration without reabsorption with low levels of tubular excretion at P-creatinine levels up to 200 µmol/L. At higher levels of P-creatinine elimination increases through tubular excretion and in faeces, thus GFR may be overestimated. At the Department of Clinical Chemistry at Laboratory Medicine, Skåne, GFR is estimated based on P-creatinine and the revised Lund-Malmö formula for eGFR$_{(Crea)}$.[14-16]

Another common advocated formula for estimating GFR based on P-creatinine was an equation developed from the Modification of Diet in Renal Disease (MDRD) study.[17]

Albuminuria and CKD

A certain degree of proteinuria is normal. Healthy people lose about 270 mg of protein per litre urine. Albumin, as a major plasma protein, can be found in trace amounts of about 42 mg per litre urine, which is considered to be normal. Thus, in clinical practice, the term albuminuria is used when the concentration exceeds the normal amount of albumin in urine. The capillary filter in the glomeruli is the crucial barrier for preventing loss of albumin to the urine. The occurrence of pathological amounts of albumin in the urine is caused by a higher permeability in the glomerular filter, due to damage from conditions such as diabetes mellitus, chronic glomerulonephritis or hypertension. Albuminuria can be quantified in mg per 24 hours collected urine representing the most accurate measure. But the collection of urine for 24 hours is cumbersome for most patients and associated with erroneous measurements, often due to incomplete collection. Alternative measurements have become established like the concentration of albumin in a single sample of morning urine (mg/L), but this may be subject to variations according to the urine volume. A method, which is generally used, is the ratio of albumin to creatinine in a single sample of morning urine. This method reduces the inaccuracy due to differences in urine volume. Thus, the urine-albumin-creatinine ratio (ACR) was established and is categorized into 3 ranges: normal <3 mg/mmol; hyperalbuminuria >3 mg/mmol, which is classified as moderate when 3 to 30 mg/mmol and severe when > 30 mg/mmol. Albuminuria is considered to have a predictive value for cardiovascular and non-cardiovascular mortality in the general population.[18, 19] In patients with chronic illness like diabetes mellitus, hypertension, cardiovascular disease and or chronic kidney disease, albuminuria is established as a prognostic factor for adverse clinical outcomes.[7, 20, 21] A 4-fold increase in urine-albumin-creatinine-ratio was associated with a 3.08 times higher risk to reach end stage renal disease, and a 4-fold decrease with 0.34 times lower risk.[22] The aetiology of albuminuria is multifactorial.[23, 24] Proximal tubular cells stimulated by albuminuria can release inflammatory, vasoactive and fibrotic substances, which have been identified as risk factors for CKD progression.[25, 26]

Physical activity and physical performance in CKD

The World Health Organization defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure. Exercise training can be regarded as a subset of physical activity. Physical activity performed as exercise training is planned, structured and repetitive. It has the objective of improving or maintaining physical performance or fitness, which can be related to general health and or ability.[27] At least 30 minutes of moderately intense exercise training 5 days per week are the recommendations of the World Health Organisation for healthy people.[28]

Physical inactivity – morbidity and mortality

Physical inactivity or the lack of physical activity has been identified as the fourth leading risk factor for global mortality causing approximately 5.2 million deaths annually.[29] The effects of physical inactivity for the development of cardiovascular disease, diabetes, cancer as well as mortality in the general population are well known.[30-33] Similar associations between physical activity and mortality have also been shown for patients with CKD.[34-38] Patients with CKD generally report a low level of physical activity and a decrease in physical activity is observed as CKD progresses.[39, 40]

The increased risk of morbidity and mortality in patients with CKD was associated with muscle weakness, especially for the elderly and for patients with dialysis DD-CKD.[41] The deterioration in physical performance did not appear suddenly once patients reached end stage renal disease and became dialysis dependent. Physical inactivity and impaired physical performance seemed to start earlier in the course of CKD and seems to be important for the progression of CKD, as well as for morbidity and mortality, as reported in observational studies.[42-46]

Physical inactivity and impaired physical performance

CKD leads to impaired muscle function and weakness, which affects strength and endurance and eventually results in impaired mobility and balance. Measuring physical function or performance and observing reductions in mobility, diminished endurance, strength, balance or other abilities can be the first step to becoming aware of an impairment and identifying people at risk for further loss of physical performance. The importance of physical performance for patients with CKD and their everyday lives became increasingly obvious when dialysis treatment was established as a chronic treatment. Many patients with CKD, especially with end stage renal disease and or DD-CKD, showed such a low level of cardiorespiratory fitness or exercise capacity that they often could hardly cope with basic household activities.[45-50] Exercise capacity in patients with DD-CKD ranged between 50 and

70% of the expected norm in age and sex matched controls.[47-49] Symptoms like general fatigue, muscular fatigue, lack of stamina, reluctance, indifference or apathy, loss of concentration, sleep disorders, nausea may be more or less pronounced as renal function decreases. Most patients feel that they have to rest in order to recover and recharge energy levels and physical fitness. Unfortunately, resting does not usually lead to improvement or fewer CKD related symptoms. Rather, resting inevitably leads to a continuous decrease in physical activity and initiates a negative spiral, which in turn leads to a progressive decline in physical performance and increased muscle weakness.

Physical performance and erythropoietin

Once renal anemia could be treated with erythropoietin, there was a substantial improvement in physical performance and quality of life.[51-55] Nevertheless, the link between physical inactivity, impaired physical performance and CKD remained.

In order to increase knowledge about physical performance and the effects of exercise training in patients with non-dialysis dependent CKD (NDD-CKD), randomized controlled trials in representative patient populations have been requested.[56-58]

Impaired muscle metabolism in CKD

Sarcopenia is defined as the loss of skeletal muscle mass and function, which physiologically begins at around 50 years of age with an annual loss of about 0.5 to 1%.[59] Muscle protein wasting and the development of sarcopenia are common in patients with CKD. Sarcopenia increases with the progression of CKD and is most pronounced in patients with DD-CKD.[60, 61] The etiology is considered to be multifactorial and factors like protein energy wasting and muscle protein imbalance, inflammation, physical inactivity, insulin resistance and growth hormone resistance, decrease in sex hormones and vitamin D disturbances, metabolic acidosis and myostatin overexpression have been demonstrated in patients with CKD and have been associated with loss of muscle mass and muscle function.[62, 63]

Sarcopenia and nutritional status

An adequate and balanced intake of nutrients and proteins in order to ascertain a sufficient energy supply is the basic requirement to prevent sarcopenia. Catabolic conditions in CKD seem to be similar to those present in cancer cachexia, starvation, insulin deficiency or septicaemia.[64] To ensure that patients have an adequate and balanced nutrition during the progression of CKD, dieticians are part of the multiprofessional team at the renal care unit. The dietician follows the patient's nutritional status and provides nutritional treatment under the direction of the patient's nephrologist.

Sarcopenia and metabolic acidosis

Metabolic acidosis is a common abnormality during the progression of CKD and stimulates the breakdown of muscle proteins resulting in loss of muscle mass.[65] The cellular mechanisms mediating protein catabolism involve suppression of insulin/insulin growth factor-1 and activation of the ubiquitin-proteasome pathway.[66, 67] Insulin resistance occurs in patients with CKD and is an important contributing factor to muscle wasting, even in patients without diabetes mellitus.[68] Patients with DD-CKD and diabetes mellitus showed an even higher degree of muscle wasting.[69] Acidosis stimulates the oxidation of amino acids and correction of the metabolic acidosis decreases protein degradation.[70] Supplementation with bicarbonate was able to counteract acidosis, improve protein- and energy intake, increase mid-arm muscle circumference and plasma albumin levels, as well as slow the rate of progression of CKD.[71]

Sarcopenia and inflammation

Low-grade systemic inflammation has been demonstrated in patients with DD-CKD as well as in the early stages of CKD. Increased levels of inflammatory markers like C-reactive protein (CRP), Interleukin 6 (IL-6) or tumour necrosis factor alpha (TNF-α) have been found and were directly linked to protein energy- and muscle wasting.[72-74]

Measurement of physical performance

Measurement of physical performance may involve a number of different aspects, such as cardiovascular fitness, endurance, muscular endurance, strength, balance and sensorimotor skills. There is no measure covering all aspects. The measurements of physiological or pathophysiological functions or integrated body system functions like aerobic capacity are usually carried out in specialized laboratories and require specific and expensive equipment as well as specialized personnel. In clinical routine it is preferable to use assessment tests, which are inexpensive and easy to perform. The results from these assessment tests help the clinician to understand a patient's functional status and disabilities. At the Department of Nephrology in Lund a test battery (*Appendix A*) was developed, which has been used over decades and which has been widely adopted by other renal care units in the Southern Health Care Region of Sweden.[75]

Cardiorespiratory fitness and overall endurance

Measurement of cardiorespiratory fitness by measuring oxygen uptake during a maximal exercise test (VO_{2max}) on a cycle ergometer or a treadmill is an example of a measurement of physiological impairment requiring specialized equipment. VO_{2max} gives a specific and objective measure of the maximal oxygen consumption or maximal aerobic capacity during an incremental exercise test representing an integrated function of the heart, lungs, circulation, muscles as well as a well-functioning nervous system. However, patients with chronic diseases and or the elderly, due to their comorbidities and disabilities, can rarely reach a level of VO_{2max}. To address these limitations alternative and modified tests can be employed. For example, maximal or submaximal exercise- or working- or peak performance capacity tests ($W_{max,}$ W_{submax}) can be used. Elderly subjects without CKD need to achieve levels of oxygen uptake of about 18 and 20 ml/kg/min or higher to be able to lead a largely independent life.[76] Levels >17.5 ml/kg/min predicted a better survival in elderly patients with DD-CKD.[77] All these tests (VO_{2max}, W_{max}) are technically complex, time intensive and costly and thus, not appropriate for monitoring physical performance as part of routine follow-up in clinical practice. Physical performance measures like walking- or stair climbing capacity tests are indicative of cardiorespiratory effects, even though they cannot replace physiological measures. Nevertheless, walking- and climbing capacity can be seen as an integrated response of a functioning body system like the cardiorespiratory system. VO_{2max} is usually not achieved during walking- or stair climbing tests. The correlation between walking capacity and VO_{2max} can vary between 0.5-0.9 in patients with chronic heart- or lung disease.[78, 79] In the review of the European Respiratory Society and the American Thoracic Society, about the walking test in chronic respiratory diseases, the 6-minute walk test was regarded as a robust test of functional exercise capacity due to its correlation with W_{max} (r=0.59-0.93).[80] Stair climbing is also widely used, especially in patients post stroke or with chronic heart- or lung disease, as a surrogate measure for aerobic- and exercise capacity.[81] Stair climbing is somewhat more demanding, requires wider joint ranges and flexibility than walking.[82] Thus, stair climbing is for relatively well-functioning patients and is also a better test for reaching a higher level of exertion. The combination of walking- and stair climbing capacity seems to correspond better to aerobic capacity than either test alone.[83, 84]

Muscular strength

Measurement of muscular strength as an expression of the muscles' physiological and neuromuscular functioning has been shown to be associated with morbidity and survival in CKD, especially in DD-CKD.[37, 77, 85] Muscle strength has been measured in almost all larger groups of muscle especially in the legs, but also in the forearms using handgrip strength.

Quadriceps strength

The largest muscle of the body, with a muscle mass of about one to two kg, is the proximal leg muscle: the quadriceps femoris. Dynamic strength can be measured as one repetition maximum (1RM), which is defined as the load required to perform one repetition only of a specific exercise.[86, 87] It is also possible to measure the load required for multiple predetermined repetitions like three, five or ten repetitions (3RM, 5RM, 10RM), as another type of measure of maximum performance [88, 89]. Instead of evaluating the load required for a maximum repetition, peak force or peak torque can be used to evaluate isometric or isokinetic contraction using a dynamometer.[90-92] These methods for measuring muscle strength are not only used for the extensors in the thigh, but can also be applied to the hamstrings, the abductors and adductors, as well as the plantar and dorsi-flexors in the lower leg, in the forearm and the hand.

Handgrip strength

Muscle strength in the forearm and the hand is mainly assessed by handgrip strength using a hand dynamometer, which measures isometric strength. Handgrip strength is often used in the context of assessing patients' nutritional status, when evaluating effects of inflammation and subsequent muscle weakness and sarcopenia. Use of the hand dynamometer is simple and can easily be integrated in an assessment tool for evaluation of patients' physical performance status in clinical routine.

An analysis of a long term follow-up of 27 years, in a non CKD population of men, showed that lower handgrip strength and body weight at baseline was associated with higher mortality.[93] The study showed a loss of handgrip strength by about 1% per year, which increased to >1.5% per year if the men were older, had lower body weight or suffered from chronic illness such as cardiovascular disease, diabetes or chronic lung disease.[93]

Loss of handgrip strength in patients with NDD-CKD has been associated with malnutrition and inflammation.[94] Strong correlations have been found between handgrip strength and lean body mass in patients with NDD-CKD 5 just before starting dialysis treatment.[85] This was reported for both men and women, with low handgrip strength being considered an independent factor associated with malnutrition in these patients.[85] Patients with NDD-CKD 1 to 5 showed associations between decreased handgrip strength and the combined endpoint of reaching DD-CKD or pre-dialysis mortality.[95] Handgrip strength decreased in patients with NDD-CKD in conjunction with the progression of CKD from stages 1 to 5.[96] At the early stages of CKD the handgrip strength was similar to that of healthy subjects.[96] In patients with DD-CKD handgrip strength was about 70% of the reference values.[97] In DD-CKD the reduced handgrip strength showed no correlation to body mass index.[98] However, a strong correlation was reported between handgrip strength and lean body mass, measured by DEXA.[99] Moreover, better handgrip strength was identified as a survival advantage for women with NDD-CKD before starting chronic dialysis treatment.[99]

Muscular endurance

Measures of muscular endurance in single muscles or muscle groups represent muscular fatigability. This can be done by recording the time an isometric muscle contraction can sustain a stable position. It can also be measured by counting the number of repetitions until muscle fatigue or by recording the time it takes to perform a number of pre-determined repetitive dynamic muscle contractions or movements, which represent functionality in a group of muscles. A pre-determined load can be derived from the repetition maximum tests as described above. Some tests use 60% of the maximum load during one repetition or 80% of the maximum load during five repetitions.[87-89, 100]

Sit to stand test (STS)

Other tests, such as the sit to stand test or the squat test measure more complex muscle functions such as number of rises from a sitting position within a predetermined time such as 30 seconds or 60 seconds (30-STS, 60-STS) or number of squats, which test the function of the proximal leg muscles.[91, 101-103] Some tests, like a form of the sit to stand test, focus on a set number of repetitions which aim to be performed as quickly as possible, for example five or ten rises from a chair (STS-5, STS-10). Such a small number of repetitions may not be sufficient to provoke muscle fatigue, instead the results indicate the power in the tested muscles.

Heel rises and toe lifts

Heel rises and toe lifts can be used to assess function, strength and endurance in the distal or lower leg muscles and are more common when following up patients after a stroke, with chronic heart or lung disease, during rehabilitation of orthopaedic disorders as well as in patients with peripheral vascular disease and or diabetes mellitus. The physical function tests often use the subject’s body weight as a pre-determined load, thus the tests also provide information on possible weaknesses of importance for activities of daily living.

Complexity of physical performance tests

For frail patients, concomitant disabilities may affect the performance of, for example, the sit to stand test, which has to be performed without any aids. Patients' balance and or coordination may affect the outcome of the test. In one study, the sit to stand test predicted for recurrent falls in the elderly, if it took longer than 15 seconds to complete five rises at maximum speed.[104] These overlapping links between tests of physical function and performance, like the sit to stand test, walking- or stair climbing tests have to be taken into account when interpreting the results. Despite a seemingly indistinctness of the more complex physical performance tests, the results provide valuable information concerning overall physical function and ability to perform activities of daily living.

Balance

The ability to maintain balance is a prerequisite for all physical performance tests and thus a more or less integrated part of each physical performance assessment test. Often one only becomes aware of balance capacity, when disturbances or impairments occur and affect or limit physical performance and or activities of daily living. Balance impairment is not always obvious, as for example being very noticeable when subjected to rotational vertigo. A well-functioning balance system requires continuous input of information from the vestibular-, the visual-, and the somatosensory or proprioceptive systems. All information is continuously processed in the central nervous system with subsequent activation of muscles to stabilize the body in either static or dynamic positions. Consequently, there are two forms of balance capacity: the static and the dynamic.

A decrease in balance capacity is associated with increasing age.[105] Conditions such as cerebrovascular disease, arthropathy or neuropathy all have an impact on balance capacity. Impaired balance predicts risk of falls, especially in the elderly and the frail.

Berg balance scale

A scale for measuring balance in older people was developed by Katherine Berg and is called Berg balance scale. The scale consists of 14 different tasks, which test functional balance performance (*Appendix B 1-3/3*).[106] Each task is evaluated using a score from 0 to 4, depending on the achieved level of performance. The individual scores are summarized and the total maximum of achievable points is 56. This test is widely used. It is standardized, validated and reliable and consists of both static and dynamic balance performance measures.

Functional reach

Dynamic balance performance measures are considered to be superior to static tests like standing on one leg. However, testing dynamic balance can be complex and can require sophisticated laboratory equipment. Fortunately, Pamela W. Duncan developed the functional reach test, which is simple to use and clinically accessible. The functional reach test has been used routinely at our department long before RENEXC started. The functional reach test is a useful tool for measuring dynamic balance using a continuous scale.[107] The functional reach test is considered to be a precise, reliable and clinically accessible. It is an age-sensitive measure of balance performance, and is recommended for prospective clinical trials.[108]

Fine motor skills

Fine manual dexterity or fine motor skills in the hands or fingers are part of functional ability in the upper extremities and decrease in relation to age.[109, 110] An intact peripheral nervous system is necessary for well-functioning fine motor skills in the hands.

Polyneuropathy

Polyneuropathy is one of the complications of CKD. Patients suffer typically from disturbances in the peripheral nervous system due to distal axonopathy. It usually starts from the most distal parts of the axons with degeneration and subsequent axonal atrophy towards the nerve's cell body. Loss of sensibility like tactile recognition or two-point discrimination may be early signs of the neuropathy. Symptoms like numbness or tingling can occur in patients with DD-CKD, but also in patients with NDD-CKD. Patients with diabetes mellitus as an underlying or concomitant disease are especially vulnerable to neuropathy.

Moberg's picking up test

Erik Moberg introduced a functional test for examining sensibility in an injured hand, the Moberg's picking up test. He concentrated primarily on the damaged peripheral median nerve in order to follow sensibility during the rehabilitation process. Median nerve compression, due to carpal tunnel syndrome, can occur in CKD especially in DD-CKD.

Moberg's picking up test has been part of the physical performance test battery at our department for many years. The test has been used in order to detect symptoms suggestive of polyneuropathy or median nerve compression. It therefore also became part of the RENEXC follow-up physical performance test protocol. Age-matched reference values are available. As it is difficult to standardize the 10 items assembled for picking up as well as the exact size and shape of the box, the test is best used to follow a patient's status.[110]

Combined physical performance measurements and test batteries

The combination of a number of single physical performance tests in a validated test battery provides a more comprehensive assessment of physical performance. All physical performance tests measure rather complex physical and more or less integrated body system functions. The distinction between measures of endurance, muscular endurance, strength, balance and fine motor skills is theoretical and some of the tests can be assigned to a number of performance measures. The sit to stand test and the stair climbing test, for example, can also be categorized as measures of strength in the lower extremity.

The short physical performance battery, which focuses on performance in the lower extremities, by measuring gait speed, sit to stand and balance, is widely used.[111]

Test battery in Lund

As previously mentioned, a test battery of physical performance measures in patients with DD-CKD was assembled and validated by the physiotherapists at the Department of Nephrology in Lund.[75] The focus was on measuring physical performance in the hands, feet, legs as well as balance, which all had been identified as functionally impaired in patients with DD-CKD.[75] In the beginning, patients with DD-CKD were assessed and given individual recommendations in order to maintain and or to improve their physical performance based on their results. The concept was then expanded to include patients with NDD-CKD 5 and patients with a kidney transplant. Based on these standardized assessment results, study I was conducted. The assessments were integrated in clinical routine and were not collected for pre-determined scientific purposes (*Appendix A*).[75]

Test battery in RENEXC

In RENEXC, the test battery already established in clinical routine (*Appendix A*) was extended with the 6-minute walk test, the 30-seconds sit to stand test and Berg balance scale (*Appendix B1-3/3*).

The 6-minute walk test, the stair climbing test, the 30-seconds sit to stand test, the heel rises test and the toe lifts test were chosen as assessment tools in RENEXC. They all represent complex and overlapping tests of physical function and performance. Despite this complexity, each physical performance test was categorized according to the main muscle function, which the test predominately assessed. The categorization of which function was measured was based on

Koufaki et al. However, her grouping was partially amended in RENEXC.[112] The 6-minute walk test and the stair climbing test were categorized as measures of overall endurance, the 30 seconds sit to stand test as muscular endurance in the proximal leg muscles and heel rises and toe lifts as muscular endurance measures in the distal or lower leg muscles.

Distribution of dominance between the right and left side

About 70 to 95% of the general population is right-handed, i.e. have a right-sided dominance including the hand, leg and eyes, leaving roughly 10% with a left-sided dominance. The non-dominant side has been estimated to have about 10 % weaker physical performance.

Borg scale

Gunnar Borg described a method of how young healthy sportsmen could evaluate their level of exertion by a simple rating scale called rating of perceived exertion (RPE), usually called the Borg scale (*Appendix C*).[113-115] The RPE has a high correlation with heart rate, aerobic capacity, lactate and ventilatory thresholds, which facilitates monitoring and follow-up of exertion levels and exercise training prescriptions.[116-118] The use of the Borg scale was successively established in patients. Initially it was only used to evaluate the level of exertion in tests of working or exercise capacity, and eventually also to prescribe the level of exertion during exercise training.[119-121] In fact, the rating of perceived exertion is a good and simple method for estimating the exertion level of physical performance. The rating summarizes different signals from the body interpreted by the exercising subject and integrating information from the exercising muscles, the cardiorespiratory- and nervous system. There are several different scales with different ranges of categories. The most common and original one consists of 15 different categories and ranges from 6 corresponding to no exertion at all to 20 corresponding to maximal exertion and exhaustion. In the middle at level 13, the subject should reach an exertion level of somewhat hard. Level 15 at is defined as hard and 17 as very hard. When evaluating cardiorespiratory exertion in healthy men, level 13 corresponds well with a heart rate of 130 beats per minute, 15 with 150 and 17 with 170 beats per minute.[113] Strength training can also be monitored and prescribed by using the RPE 6-20.[122]

Metabolic equivalent of tasks (MET)

MET is the abbreviation for Metabolic Equivalent of Tasks or only Metabolic Equivalent and measures the energy needed to perform a physical activity. MET is defined as the ratio of energy consumption per kg body weight and hour (1 MET = 1 kcal/kg/h = 4.184 kJ/kg/h). One MET is defined as the resting metabolic rate or the energy expenditure during sitting still. Physical activity can be expressed in relation to one MET. Thus, sleeping is considered to be 0.9 MET, watching television 1.0, doing paperwork 1.8 and walking at a pace of 3 km/h 2.4. Low intensity physical activity is defined as MET levels < 3 kcal/kg/h. Moderate intensity is categorized as MET between 3 and 6 kcal/kg/h. Cycling at 50 W corresponds to 3.0 MET and at 100 W to 5.5 MET, walking at 5 km/h corresponds to 3.3 MET and home exercise training at a level defined as somewhat hard to between 4 and 6 MET. High intensity physical activity is defined as > 6 kcal/kg/h and comprises activities such as jogging or running, which correspond to 7 or 8 MET, while intensive exercise training like push-ups, sit-ups or jumping jacks correspond to about 8 MET.

Frailty in CKD

Frailty is a term used in geriatrics and is associated with aging and people older than 65 years. Frailty is a chronic syndrome and involves 5 dimensions, which have to be assessed: unintentional weight loss, poor endurance or exhaustion, muscle weakness, slowness while walking and low levels of physical activity. Frailty is identified if ≥ 3 dimensions are present; 1-2 dimensions are defined as pre-frail. Weight loss is defined as unintended loss of weight of ≥ 4.5 kg or ≥ 5% of body weight during the last year. Poor endurance is present when every movement is experienced as an effort or an inability to walk due to the effort being too great for ≥ 3 days during the last week. Muscle weakness is present if handgrip strength is < 20% of the expected norm. Slowness while walking is present if the time it takes to walk 15 feet (=4.572 m) is 20 % longer than the expected norm. A low level of physical activity is defined as leisure time activity which is less than 20% of the expected energy expenditure.[123] The frailty assessment has been modified, however all assessments are based on the original one and the adjustments are often adaptations to available data.

Frailty - epidemiology in CKD

The prevalence of frailty in people ≥ 65 years is about 7%.[123, 124] In a cohort of 40 000 women between 65 and 79 years, about 16% were defined as frail.[123, 124] Frailty among patients with DD-CKD has been reported to be 68%. Even among patients younger than 40 years 44% are defined as frail and 50% in 40 to 50-year olds. Frailty was associated with greater comorbidity and frail patients had nearly twice as high a risk of death or hospitalization per year.[125]

In a cohort of 1 111 patients with NDD-CKD and a median eGFR of 49 ml/min/1.73m^2 7% were classified as frail and 43% as pre-frail, which corresponded to a decrease in physical performance assessed by the Short Physical

Performance Battery (SPPB).[126] In an analysis of 812 patients participating in the MDRD study (Modification of Diet in Renal Disease), with a mean measured GFR of 33 ml/min/1.73m^2 and self-reported symptoms of frailty, 16% of the patients were defined as frail and 53% as pre-frail.[127] The most common dimension of frailty was low physical activity in 47% of the patients, followed by poor physical function in 23%.[127] Moreover, the frail patients had a higher mortality.[127]

The first exercise training studies in CKD

In the 1970s and 1980s pioneers recognized the potential of physical activity and exercise training for patients with CKD. The very first studies were from the USA and Germany in patients with DD-CKD.[128-131] Patients were both assessed and conducted their exercise training sessions using a cycle ergometer or treadmill. These early studies showed that patients on maintenance dialysis could improve their working capacity or cardiovascular reserve after exercise training.[131] Goldberg et al. showed metabolic and psychological effects of exercise training in patients with DD-CKD as well as improved hypertension and reduced coronary risk.[129, 132, 133] Painter et al. showed that patients with peritoneal- and hemodialysis as well as transplant patients had reduced exercise capacity, which, however, could be improved by exercise training.[48, 49] Clyne et al. showed that patients with NDD-CKD had reduced working capacity, which decreased as GFR declined and improved after renal transplantation.[45, 134] In the first exercise training study in patients with NDD-CKD, Clyne et al. showed that working capacity and muscle strength and endurance in the legs increased significantly after three months of regular exercise training compared with a sedentary control group.[100] These early studies were usually controlled but not randomized, characterized by few participants, who were highly selected, and mostly comprised of patients with DD-CKD.

Randomized controlled trials (RCTs) - exercise training in CKD

A randomized controlled trial (RCT) is a study with the objective to investigate efficacy of an intervention by comparing two groups. The trial can comprise two treatment arms or one treatment arm and a control arm. Patients are randomized according to a predetermined allocation key to avoid selection bias. These studies typically include predetermined criteria for: inclusion and exclusion, hypothesis, outcome measures, methods, structured monitoring and follow-up as well as statistical analysis. Observational and non-randomized controlled designs are subject to potential bias and confounding due to lack of comparability, risk of observer or selection bias. Thus, the RCT is the gold standard for proof of concept.

Initial exercise training RCTs

One of the first randomized controlled exercise training trials in patients with DD-CKD showed an improvement in working capacity by about 20% after 8 months of exercise training.[129] Furthermore, there was a reduction in antihypertensive medication and a decrease in the use of phosphate binders; hemoglobin increased by 37%, glucose levels improved and hyperinsulinism decreased; triglyceride levels decreased and HDL increased and there were also signs of fewer depressive symptoms.[129] When erythropoietin became available to patients with DD-CKD and renal anemia could be treated working capacity improved.[51, 52, 135, 136] Further improvement in working capacity was observed when exercise training was added to the treatment of anemia in DD-CKD.[88, 137, 138]

Exercise training RCTs in CKD – in general

To date, about 70 RCTs have been published investigating effects of exercise training on physical performance in patients with CKD. The majority, comprising about 70% of the trials, focused exclusively on aerobic or endurance exercise training effects consisting of 30 to 90 minutes per session mostly three times per week at an exertion level of 60 to 80% of VO_{2max}. Strength exercise training only or a combination of strength and endurance exercise training constitute equally the remaining 30% of the trials. In over 75% of all the exercise training RCTs, patients with DD-CKD, mainly on hemodialysis, were investigated. Patients with NDD-CKD have participated in about 15 trials and are subsequently underrepresented, especially, in view of the fact that patients with NDD-CKD represent about 90% of the whole CKD-population. Thus, one could presume that it would be worthwhile for programs to focus on prevention and or life style interventions, principally in terms of improved physical activity or exercise training and nutrition in the NDD-CKD population.

Intervention periods - exercise training RCTs in CKD

The intervention period in the majority of the RCTs was 12 weeks, sometimes extended to 16 and up to 20 weeks. More than 80% of all exercise training RCTs were conducted within a period of 6 months. Longer intervention periods involving 12 or more months are very rare comprising about 10% of the trials. Three of these long term RCTs have been performed in patients with NDD-CKD.[139-141]

Non-exercising control groups

More than 80% of the studies randomized participants either into an exercise intervention group or into a comparison group, who received usual care or had a continued sedentary lifestyle. Comparison of different intervention groups without using non-exercising controls has only been conducted in a few studies.[142-145]

Number of exercising participants

The number of patients participating in exercise intervention groups in the RCTs in about 80% of all trials is limited to between 6 and 25 patients. Studies with more than 40 exercising participants are very rare and were mostly performed in patients with DD-CKD and limited to a 6 months intervention period.[102, 144, 146] The highest number of exercising participants in an exercise training RCT in patients with NDD-CKD was 36 during a 12 months intervention period.[141, 147] In the study by Rossi et al., 59 patients with NDD-CKD were investigated, but the intervention period was limited to 12 weeks.[148]

Choice of physical performance assessment

Most RCTs assessed physical performance and measured aerobic or working capacity. Thus, more than half of all patients with CKD who participated in these exercise training RCTs (comprising about 650 patients in total), had to perform a treadmill or cycle ergometer test to be able to participate in the trials at all. Subsequently, the choice of the physical performance assessment test restricted the participants to patients who were able to perform these tests. In consequence, most older and frail patients, who make up the majority of patients with CKD, have been systematically excluded. Thus, both the representativeness of the participants for the whole CKD population and the generalizability of the results might be considered to be limited.

Exercise training RCTs and physical performance assessments in clinical routine

RCTs using easier to perform physical assessments can widen the spectrum of participation to the more comorbid and partially frail elderly and thus, a better representativeness and generalizability may be achieved. Such RCTs comprised in total approximately 600 patients, of whom only about 11% were patients with NDD-CKD.[86, 148-150] The longest observation time in that group was 24 weeks.[150]

To date, the most important exercise training RCT is the multi-centre trial, EXCITE, conducted in patients with DD-CKD using a simple intervention consisting of a personalized home based walking exercise program for 6 months.[102] Physical performance was assessed by the 6-MWT and by the STS-5. The exercise group consisted of 151 patients.[102] The exercise group improved their walking capacity from 328 m to 367 m and the time in the sit to stand test from

20.5 to 18.2 seconds.[102] The usual care control group had unchanged walking capacity and leg strength.[102]

Balance – assessment and or training in RCTs in CKD

Direct assessment of balance in exercise training RCTs is exceedingly rare. In some studies, static balance was assessed as part of a combined physical performance assessment score like the Short Physical Performance Battery (SPPB) or the Groningen Fitness Test for Elderly.[145, 151] These studies investigated patients with DD-CKD. In the RCT using the SPPB score, improvements were reported after 24 weeks of a low intense strength exercise training program during dialysis.[145] Balance training exercises to improve or maintain both, static and or dynamic balance capacity, have not been reported in exercise training RCTs in patients with CKD.

To summarize, there are not many randomized controlled trials with exercise training or rehabilitation programs for patients with CKD, especially not for patients with NDD-CKD. In the existing RCTs the majority of patients with CKD, i.e. older and more frail patients, are usually underrepresented. The RCTs are mostly limited to small numbers of participants and generally have short intervention periods. Implementation or integration into clinical routine and follow-up of the patients is usually absent. Thus, taking these circumstances into consideration, exercise training RCTs are required.[56-58]

Effects of exercise training RCTs on physical performance in CKD

Endurance or cardiorespiratory effects

RCTs investigating aerobic or working capacity as the outcome measure showed almost consistently improvements, regardless of the exercise training intervention. The interventions could be endurance- or aerobic exercise training only or in combination with strength- or resistance exercise training. The cardiorespiratory effects showed improvements in VO_{2peak} by about 20%, ranging from about 8% after 16 weeks of supervised aerobic- or endurance exercise training at an exertion level of 50 to 60% of VO_{2peak} up to increases in VO_{2max} of 43% after 6 months of aerobic exercise training three times per week in patients on hemodialysis.[152, 153] Aerobic or exercise capacity improved regardless of training intensity, length of intervention, or if there was supervision or not. Both high and low intensity endurance exercise training affected aerobic capacity positively, with a more pronounced effect with high intensity as shown by Painter et al. 2002.[138] Significant improvements were reported after three months, after 4 to 6 months and after 7 to 12 or more months.[56-58] The effects were most pronounced after 4 to 6 months.[56-58]

Aerobic or exercise capacity and endurance measures

Some RCTs assessed both physiological measures of aerobic or working capacity and others used more clinical practical measures, as for example walking- or stair climbing capacity. As mentioned earlier, walking and stair climbing assessment tests widened the possibility for participating in exercise training trials, even for older patients with CKD. In consequence, patients participating in RCTs in which aerobic- or working capacity was the main test used were usually younger than 60 years of age. In contrast, studies, which did not test aerobic capacity, had older patients with CKD, whose ages were between 68 and 71 years. The exercise training interventions in these studies were safe and improved physical performance.[145, 148]

Walking capacity

A walking capacity test using the 6-MWT was the predominant test in the elderly patients. These studies showed improvements ranging from 6% to 19% after endurance exercise training or a combination of endurance and strength exercises, regardless of age and intervention time.[148, 150] An exercise training trial in patients with CKD 3 and 4 and a mean age of 69 years increased walking distance from 325 m to 396 m in the 6-MWT after three months of intervention.[148] The program consisted of two exercise training sessions per week, was centre based and in a group setting with both endurance and strength exercise training.[148] Endurance training was monitored by the level of rating of perceived exertion corresponding to an exertion level of 60 to 65% of the predicted maximal heart rate. The specifically trained staff encouraged the patients to increase their exertion gradually at each session.[148] In contrast, a relatively well functioning and younger dialysis population with a mean age of 55 years maintained their walking distance after 12 weeks of combined intradialytic endurance and strength exercise training, but improved their submaximal working capacity and muscle strength.[88]

Muscular strength and endurance effects

Generally, muscular strength is improved by regular exercise training in patients with CKD, regardless of training modality, intensity, time of intervention period or whether patients are supervised or not.[56-58] Most RCTs studied patients with DD-CKD, only a few included patients with NDD-CKD. Regular exercise training for three up to 6 months increased muscular strength, regardless of training modality, i.e. endurance, strength or combined endurance and strength exercise training.[56-58] To date RCTs investigating the effects of exercise training on muscular strength have had an intervention period of at most 7 months.[56-58]

Effects on quadriceps femoris

Strength in the proximal leg muscles, measured by RM in patients with DD-CKD, almost doubled after three months of combined strength and endurance exercise training compared with baseline.[88, 154] Improvements of about 20% could be found, with dynamometer measurements, after 12 weeks and 20 weeks, respectively, of endurance or strength exercise training.[154, 155]

Effects on handgrip strength

Handgrip strength, in the RCTs, was generally found to be maintained irrespective to exercise training modality.[141, 146, 156] In the to date only study investigating strength effects in patients with NDD-CKD by Howden, handgrip strength was maintained, as was the timed up and go test, which was used as a measure of muscle power.[141]

Effects on muscular endurance

Muscular endurance, measured with 60-STS and 30-STS, was generally improved after either three or 6 months supervised endurance exercise training in patients with DD-CKD.[101, 144, 157, 158] Koufaki et al. showed also improved exercise capacity after three months of endurance exercise training in DD-CKD.[101] She also reported maintained physical performance in the North Staffordshire Royal Infirmary test, which is a combined test of physical performance including walking and stair climbing.[101]

Muscular endurance measured as 30-STS was also assessed in patients with NDD-CKD.[103] The patients were at mean age of 56 years and both muscular endurance, measured as 30-STS, and VO_{2max} were assessed and improved after three months of intervention.[103] The exercise training consisted of endurance training three times per week for 30 minutes, which was increased by ten minutes after 4 and 8 weeks, respectively.[103] The intensity was prescribed according to the ventilatory threshold, assessed by the cardiopulmonary exercise test, and set at an estimated 40 to 60% of VO_{2max}, which corresponds to a mild to moderate exercise intensity.[103] The trial showed an improvement in 30-STS from 17 to 24 chair rises within 30 seconds, as well as improved cardiorespiratory parameters, walking- and stair climbing capacity.[103]

Rossi et al. also measured repetitions of arm curls, which increased after the intervention period from 18 to 23 within 30 seconds.[148] This study is, to my knowledge, unique in measuring muscular endurance in the upper arm in patients with CKD in a RCT.[148]

Effects on power

As mentioned before, the sit to stand test can also be used to measure strength and power by measuring the time it takes to perform 5 or 10 repetitions as fast as possible (STS-5, STS-10). Squats performed as fast as possible (squats-10) may also belong to this category. Patients with NDD-CKD and a mean age of 69 years could shorten the time by an improvement of about 29% in STS-10 after combined endurance and strength exercise training for 12 weeks.[148] Other RCTs assessing STS-5, STS-10 or squats-10 were conducted in patients with DD-CKD, who shortened the period of time by about 15 to 20% after five to 6 months of endurance exercise training.[144, 157-159] Patients with DD-CKD who performed strength exercise training for three months maintained their results in STS-5.[154] In another study, patients with DD-CKD at a mean age of 71 years improved their STS-5 and shortened their time by about 16% after 6 months of strength training.[145] The combination of strength and endurance exercise training resulted in an improved performance time of about 22% in STS-10 after three months in 52 years old patients with DD-CKD.[151]

Other important exercise training effects in CKD

Earlier studies have shown positive effects of exercise training on the heart with improvement in left ventricular mass index, cardiac output and ejection fraction as well as improved heart rate variability or lower arrhythmia rate.[152, 160] Improved blood pressure control has been reported after 4 and 6 months of exercise training in patients with NDD-CKD.[161, 162] Antihypertensive medication could be reduced in patients with DD-CKD after 6 months of regular exercise training.[163] Cycle ergometer exercise training in patients with DD-CKD improved lipid status, glucose elimination and insulin sensitivity after 12 months.[129]

Health related quality of life

Quality of life was shown to be improved after exercise training in patients with DD-CKD, patients reported fewer symptoms of depression and bodily pain, as well as increased self-perceived physical performance.[159, 164-166]

Muscle and inflammation

Strength exercise training in patients with NDD-CKD has been shown to induce muscle hypertrophy and decrease inflammation with lower levels of CRP and IL-6.[149] Both strength training and the combination of endurance and strength exercise training has been reported to reduce CRP levels in patients with DD-CKD after 8 and 12 weeks of intervention, respectively.[90, 167]

Kidney function

Experimental studies in uremic rats showed that exercise training slowed down decline in GFR.[168, 169] Some studies in patients with CKD, not randomized controlled, demonstrated improvement in GFR after 12 and 20 weeks of endurance exercise training.[170-172] Randomized controlled trials investigating GFR as an outcome measure, comprising between 7 and 15 patients with NDD-CKD per group with few exercising participants, showed no effects on GFR compared with the controls.[86, 139, 162, 173] In a group of obese diabetic patients who performed endurance exercise training for 24 weeks, in addition to improved resting blood pressure, 24 hour proteinuria was reduced.[162] Greenwood at al. reported a slower GFR decline in 10 exercising patients with NDD-CKD in a pilot RCT after combined endurance and strength exercise training for 12 months.[140]

Exercise training has been shown positive effects on proteinuria with decrease in proteinuria by low intensity swimming exercise training 30 minutes twice per week in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) after 12 weeks.[170]

Exercise training in CKD in clinical practice

Patients' physical function and disabilities were the focus of former nephrologists and physiotherapists at the department of Nephrology in Lund, when they initiated regular assessment and follow-up of functional status and physical performance in patients with DD-CKD, and later on in patients with NDD-CKD.[75]

The department has had a multi-professional team consisting of a nephrologist, a kidney failure nurse, a physiotherapist, a dietician and a clinical social worker for many years. One of the team's objectives is to motivate each patient to maintain or to improve his/her autonomy as far as possible. The team works to enable patients to live as independently as possible for as long a time as possible, despite suffering from a severe and chronic illness such as CKD.

Physical performance assessment in CKD in clinical routine

Historically, patients have been assessed just before start of dialysis and were recommended exercise training according to the results of the physical performance test battery. Despite this approach, no convincing statistically significant results were found 18 months after having been recommended exercise training.[174] These results led to earlier assessment, starting when patients were registered on the department's uremia list, usually when the eGFR was 30ml/min/1.73m^2 or less. At that stage patients were recommended to start exercising and given an individualized exercising training program.

Considerations concerning exercise training in clinical routine

Recognizing the potential benefit of physical activity and exercise training should become an integrated part of all health care professionals' interactions with each patient. If exercise training is to become part of routine treatment of CKD, it needs to be individualized. Furthermore, patients need a systematic and regular follow-up rather than simple recommendations if they are going to take the program seriously and be compliant.[150] By introducing patients to thinking in terms of exertion levels and using the Borg scale for rating of perceived exertion, patients acquire an instrument for self-perceiving and self-administration of their level of exertion. Regular and frequent follow-up contacts by telephone calls as well as consultations with their physiotherapist, when necessary, would most probably improve motivation, interest, adherence and effectiveness of the rehabilitation program. The patient should decide when and where to train as long as they adhere to the main menu. To keep diaries may also contribute to encourage and motivate as well as to evaluate. All these aspects have been taken into account when planning the prospective randomized controlled clinical trial RENEXC.

The evidence about the importance of physical performance for patients with CKD is still quite low. It is still uncommon for patients to have their own exercise training plan. Furthermore, structures for monitoring and follow-up of physical performance and physical activity are still not established in renal care units. In Sweden, all larger renal care units have physiotherapists included in the multiprofessional team. Rehabilitation programs focus mostly on patients with DD-CKD, patients with kidney transplants or patients with CKD who are eligible for kidney transplantation.

It would be preferable and would provide better care, if patients with CKD at stages 4 and 5 are treated at renal care units by nephrologists, that would also facilitate registration in the Swedish Renal Registry. Consequentially, patient data can be collected from the different departments in Sweden and can be evaluated in terms of epidemiology and or quality standards. Moreover, adding some simple assessments of physical performance would provide a good opportunity of quality control and forward further studies.

Aims

The overall aim of this thesis was to investigate the importance of physical performance for patients with chronic kidney disease (CKD).

The specific aims were:

- To investigate the relationships between survival, after starting chronic dialysis treatment, and measures of physical performance, assessed prior to start of chronic dialysis treatment in a retrospective study (**Study I**).
- To investigate the relationships between GFR (glomerular filtration rate) and measures of physical performance in patients, representative of a non-dialysis dependent CKD population, in a cross-sectional analysis of baseline data from RENEXC (**Study II**).
- To investigate and compare 12 months of self-administered, individualized and regular strength- or balance exercise training, both combined with endurance exercise training on physical performance in patients representative of a non-dialysis dependent CKD population in a randomized controlled clinical trial, RENEXC (**Studies III and IV**).
- To investigate and compare the effects on GFR and albuminuria after 12 months of self-administered and regular strength- and balance exercise training, both combined with endurance exercise training in patients representative of a non-dialysis dependent CKD population in a randomized controlled clinical trial, RENEXC (**Study IV**).

Methods and Patients

This is a summary of methods used and patients participating in studies I to IV. More detailed information can be found in each paper.

Study I - a retrospective study

Study I was a retrospective study, using medical records and data from the Swedish Renal Registry. We investigated the relationship between survival and physical performance in 134 patients with CKD 5, who started chronic dialysis treatment between 1998 and 2006.

Patients >18 years of age were included and who had been assessed by the physiotherapist at the earliest one year before and at the latest 100 days after starting chronic dialysis treatment. Physical performance was measured using a standardized test protocol according to clinical routine at the Department of Nephrology in Lund (*Appendix A*).[75] The physical performance measures comprised handgrip strength, isometric quadriceps strength, heel rises, toe lifts and functional reach.

Comorbidity for each patient was calculated using the Davies' comorbidity index.[175] Blood chemistries and laboratory analyses were collected from patients' records. Patients were grouped according to survival at the end of the observation period, and factors affecting survival were analysed.

Ethical considerations

The study was approved by the Regional Ethical Review Board in Lund (ref 2012/246) and adhered to the Helsinki declaration. As the study was retrospective, patients were informed of their inclusion with an advertisement in the journal of the Skåne Kidney Patients Association (a local branch of the Swedish Kidney Patients Association). They were given the option to contact me, Matthias Hellberg, if they did not want to participate.

RENEXC - RENal EXerCise – a randomized controlled clinical trial

Study design

RENEXC is a Randomized Controlled parallel group clinical Trial (RCT) registered as NCT02041156 at www.ClinicalTrials.gov. The trial had two active treatment arms: strength - or balance exercise training, both in combination with endurance training.

151 Patients with NDD-CKD were randomly assigned to either the strength- or the balance group. Both groups were prescribed 150 minutes per week self-administered exercise training for an intervention period of 12 months. The strength group was prescribed 90 minutes strength exercise training in combination with 60 minutes endurance exercise training per week; the balance group was prescribed 90 minutes balance- in combination with 60 minutes endurance exercise training. Patients with eGFR predominantly < 30 ml/min/1.73m^2 are meant to be registered on the uremia list at the outpatient clinic of the Department of Nephrology at Skåne University Hospital in Lund. Our intention was to provide the opportunity for all these prevalent and incident patients to participate in RENEXC, irrespective of age and comorbidity, and we asked them if they were interested. After which the patients were screened according to the inclusion and exclusion criteria until at least 150 patients had been included.

According to the department's policy, each patient with an eGFR < 30 ml/min/1.73m^2, should be followed by his/her nephrologist and a renal failure nurse, according to evidence-based management of CKD, and is offered consultation and follow-up by a physiotherapist, a dietician and a clinical social worker under the direction of the nephrologist. In RENEXC, a special research physiotherapist was employed, who was responsible for the physical performance assessments, the exercise training prescription, registration of the results, and coordination of the other investigations in cooperation with the regular renal failure nurses and the medical secretary. The regular dietician assessed each patient's nutritional status. She recommended adjustments, if necessary, according to the CKD stage and or according to changed energy expenditure during the exercise training program under direction of the nephrologist. Each patient kept his/her regular nephrologist at the outpatient clinic. Routine monitoring and follow-up were conducted as usual and according to the regular doctor's direction. The clinical social worker assessed the socioeconomic status of each patient in order to establish contact, to identify problems and to support the patient in finding a solution.

Ethical considerations

The RENEXC trial was approved by the Regional Ethical Review Board in Lund (ref 2011/369) and adhered to the Helsinki declaration. All patients were informed both orally and in writing and signed a written informed consent prior to inclusion. The Swedish Nephrological Society and the Swedish Kidney Patients Association recommend physical exercise training to patients with CKD. These recommendations are part of usual care at our Department of Nephrology in Lund. To recommend patients not to do exercise training by being randomized to a sedentary control group was considered to be neither practically nor ethically feasible. Thus, RENEXC was designed to comprise two treatment arms with the same weekly training amount, the same assessment procedures and follow-ups as well as the same attention to each participant by the whole multiprofessional team.

Inclusion criteria

Inclusion criteria were kept as open as possible in order to allow any interested patient to participate, provided the age was ≥18 years and there was no contraindication for regular exercise training or other barriers to study participation. Any comorbid burden was explicitly accepted if it did not constitute a potential risk to the patient's health, as our goal was to achieve as representative a CKD study population as possible.

Exclusion criteria

Exclusion criteria were severe orthopaedic or neurologic disorders, unstable cardiovascular disease, uncontrolled hypertension, severe anemia, severe electrolyte disturbances, inability to communicate in Swedish, understand oral instructions and expected to start renal replacement therapy within one year after recruitment.

Power calculation

To detect a difference of at least 60% of the standard deviation at a 5% significance level and 80% power, we calculated to include 50 patients in each group. In order to compensate for a dropout rate of about 30% we decided to include at least 75 patients in each group.

Comorbidity

Comorbidity was assessed with the Davies' Comorbidity Score [175] at the time of the visit and physical examination prior to inclusion, performed by me, Matthias Hellberg.

Randomization

Randomization was generated by a computer program (SAS Proc Plan, SAS Institute Cary NC). Recruitment staff, including each patient's doctor, were blinded to randomization. Only the research physiotherapist and the randomized patient were aware of which training group they belonged to.

Intervention

The exercise training prescription was based individually on each patient's physical performance level and was provided by the research physiotherapist. The goal was to achieve 150 minutes per week of exercise training for 12 months. The number of sessions should be between three to five times per week and preceded by about 10 minutes warm-up. The exercise training was self-administered at home or at a nearby gym, depending on individual preferences. Each patient was intended to train endurance for 60 minutes per week, and 90 minutes per week of either strength or balance. Each patient was advised to evaluate his/her training performance by the Rating of Perceived Exertion (RPE) using the Borg scale.[115] Each patient was given a training diary (*Appendix D*) and asked to regularly report their exercise training frequency, duration and intensity by posting the diary to the physiotherapist. Weekly phone calls by the physiotherapist during the first three months, followed by every second week during months 4 to 12, were provided to monitor progress, to encourage and to adjust the training plan in order to maintain the level of exertion.

Endurance exercise training

The prescription for endurance training was at least 90 minutes (30 minutes x 3) per week at a RPE 13-15 by e.g. walking, jogging, cycling etc. and adjusted by increasing the speed, the distance or by interval training.

Strength group

The strength group was additionally prescribed 60 minutes (30 minutes x 2) per week at a RPE 13-17 per exercise set. 4 to 6 different exercises (e.g. quadriceps extension, squats, biceps curls, pull ups etc.) were performed as 2 to 3 sets of 10 repetitions and adjusted by heavier weights or the complexity of the exercise (e.g. adjusted body position regarding angle or leverage).

Balance group

The balance group was additionally prescribed balance training of 60 minutes (30 minutes x 2) per week at a RPE 13-17 per exercise set. 4 to 6 different exercises (e.g. standing with the feet together, on one leg, on a balance board or planking) were performed as 2 to 3 sets of 10 repetitions and adjusted by increasing the complexity (e.g. adding arm movements, closing eyes or changing body position).

Physical performance assessment

Physical performance was assessed by the research physiotherapist with the following tests:

Overall endurance

- 6-minute walk test (6-MWT): walking as fast as possible along a marked indoor corridor and recording the distance walked during a period of 6 minutes (walking capacity).[176]
- Stair climbing: counting the number of flights of stairs ascended or descended. One flight of stairs consisted of 10 steps. One step was 16 cm in height and 32.5 cm in depth (climbing capacity).[75]

Muscular endurance and fatigability in the proximal muscles of the lower extremities

- 30-seconds sit to stand (30-STS): the number of times rising up from a chair and sitting down again within 30 seconds.[177]

Muscular endurance and fatigability in the distal muscles of the lower extremities

- Heel rises: standing against a wall and repeatedly getting up on tiptoe and down again until fatigue, related to the normative value of 25 heel rises (the cut-off value).[75, 178, 179]
- Toe lifts: standing against a wall with the heels on the floor moving the forefoot up and down until fatigue, related to the normative value of 20 toe lifts (the cut-off value).[75]

Muscular strength and or neuromuscular function in the upper extremities

- Handgrip strength, right and left, measured by using a Jamar dynamometer. The mean value was calculated from three consecutive measurements for each hand.[75, 180]

Muscular strength and or neuromuscular function in the lower extremities

- Isometric quadriceps strength*,* right and left, measured by extending the knee against resistance, measured by kilograms multiplied by centimetres. The mean value was calculated from three consecutive measurements in each leg.[75, 92]

Balance

- Functional reach: leaning forward as far as possible without losing balance and recording the distance in centimetres.[75, 107, 181]
- Berg balance scale: 14 simple balance related tests, e.g. standing up from a sitting position or standing on one foot and scoring each task from zero (unable) to four (independent). The maximum score is 56 comprising the sum of all scores *(Appendix B 1-3/3)*.[182]

Fine motor skills

- Moberg's picking-up test: picking up 10 different small items (four bolts, one hexagon nut, one wing nut, one coin, one bottle cap, one paperclip and one safety pin) from a leather pad (area: A4=210mm x 297mm) on a table and putting each item, one at a time, into a plastic box (size: 10 x 10 x 3 cm), and recording the time, performed for each hand with open and closed eyes, respectively.[75, 183]

Tests of stair climbing, heel rises, toe lifts, isometric quadriceps strength, handgrip strength, functional reach and the picking-up test are part of the routine physical performance assessment in patients with CKD in the Southern Region of Sweden, which has been used for about 20 years and has been tested according to reliability and validity.[75]

Training intensity and adherence

Training intensity and adherence during the 12 months of intervention was addressed by evaluating the reported training time and RPE in the training diaries. Cumulative and weekly average values were calculated.

Laboratory analyses

Laboratory analyses were performed at baseline and after 4, 8 and 12 months of intervention by routine methods at the department of Clinical Chemistry, Laboratory Medicine Skåne in all studies.

Iohexol clearance - mGFR

Iohexol clearance was measured at baseline and after 12 months of intervention in order to obtain a measured GFR so as to eliminate creatinine and muscle mass related confounders. The measurement is established at the department of Clinical Chemistry, Laboratory Medicine Skåne, used in clinical routine and requested by our and other clinics several times a week. The laboratory requires an up-to-date body weight and P-creatinine (not older than one month) for estimation of GFR. The patient is given an intravenous injection of 5 ml iohexol (300mg iodine/ml, 647mg iohexol/ml). GFR is calculated based on the amount of iohexol injected, the estimated distributions volume of iohexol (calculated on the basis of body weight) and the concentration of iohexol in the blood sample taken. In patients with CKD, the blood sample is taken according to the estimated GFR (eGFR). If the eGFR is between 20-50ml/min/1.73m^2 the sample is taken 7 hours after the iohexol injection, if it is <20ml/min/1.73m^2 the sample is taken 24 hours after the injection. Iohexol concentration is measured by high performance liquid chromatography.

Study II - a cross sectional study (RENEXC substudy)

This was a baseline data analysis collected from the RENEXC-trial after 151 patients had been screened and 101 patients had been included.

Renal function was presented as measured glomerular filtration rate. We did not group according to CKD stages in order to avoid so as inaccuracy for observations especially for GFR, around the transition areas.

Study III - a randomized controlled clinical trial (RENEXC substudy)

This RENEXC substudy was conducted between October 2011 and May 2016 after 217 patients had been screened and 151 patients had been included. The effects of 4 months of exercise training on measures of physical performance were assessed.

Study IV - a randomized controlled clinical trial (RENEXC)

The RENEXC study was conducted between October 2011 and May 2017 after 217 patients had been screened and 151 patients had been included. The effects of 12 months of exercise training on physical performance measures, iohexol clearance and urine-albumin-creatinine-ratio were assessed.

Statistical methods

Continuous variables are presented as means ± standard deviations and or 1st - 2nd - 3rd quartiles. Categorical variables are given as percentages and frequencies. A p-value <0.05 was considered statistically significant. Effects are presented as estimates and with 95% confidence intervals. Data were analysed using the R-software (www.r-project.org).

Study I

Hazard ratios in univariate survival analysis were used to detect and quantify significant differences between the deceased and alive group. Subsequent multivariable analyses as proportional hazards or Cox regression were used to adjust for confounding variables.

Study II

Multivariable linear regression analysis of different endpoints comparing each physical performance measure included the predetermined explanatory variables: mGFR, sex, age, comorbidity and the interaction between sex and age.

Studies III and IV

Intention to treat analysis was used to compare the two exercise groups and all randomized patients were included. To address missing data, we chose the mixed model analysis.

Physical performance measures at baseline and at 4 months (study III) were evaluated using the following effects: time, treatment and their interaction as fixed effects and subjects as random effects.

Physical performance and kidney function measures at baseline and at 12 months (study IV) were evaluated using the main effects: time, treatment and their interaction as fixed effects and subjects as random effects.

Results

Study I – survival and physical performance in CKD 5

During the median follow-up time of 3.5 years 112 of 134 patients were alive at the end of the observation period and were compared with the 22 deceased patients. Older age at start of dialysis treatment was related to higher mortality. No significant differences between the two groups could be seen concerning sex, eGFR, comorbidity, weight, height or laboratory data. When grouping low comorbidity (i.e. none or 1 comorbid domain) together, the deceased group showed higher comorbidity. Table 2. shows the general clinical characteristics for the alive and deceased group separately, both groups combined as well as the significances after comparison between the alive and the deceased group after.

Table 2.
General clinical characteristics – study I

Clinical characteristics	Units	Alive (N=112)	Deceased (N=22)	Combined (N=134)	P
Women/Men		29/83	3/19	32/102	0.2
Age (years)	years	58±16	70±13	60±16	**<0.001**
eGFR	ml/min/1.73m^2	12±4	12±4	12±4	0.9
Comorbidity					0.07
0		13 (12%)	0 (0%)	13 (10%)	
1		78 (70%)	14 (64%)	92 (69%)	
2		21 (19%)	8 (36%)	29 (22%)	
Weight	kg	80±15	79±18	79±16	0.9
P-Creatinine	μmol/L	501±202	464±122	495±191	0.6
P-Urea	mmol/L	27±8	47±76	30±33	0.08
C-reactive protein	mg/L	10±17	9±9	10±16	0.5
P-Albumin	g/L	34±5	34±4	34±5	0.7
Hemoglobin	g/L	114±19	112±16	114±18	0.6
Base excess	μmol/L	(-3)±4	(-1)±4	(-3)±4	0.1
P-Calcium	mmol/L	2.3±0.2	2.3±0.2	2.3±0.2	0.3
P-Phosphate	mmol/L	1.6±0.4	1.5±0.3	1.6±0.4	0.4
Parathyroid hormone	pmol/L	24±17	20±16	23±17	0.4

Mean± standarddeviation; eGFR=estimated glomerular filtration rate, based on MDRD (Modification of Diet in Renal Disease)[17]; P=plasma.

Some physical performance measures were significantly different between the groups. The deceased group had significantly lower values for handgrip strength right and left, heel rises right and left and functional reach in univariate analyses, as shown in table 3.

Table 3.
Group differences in physical performance in univariate analyses - study I

Physical performance			Alive	Deceased	P
Handgrip strength	(kg)	right	83±22	70±21	**0.017**
		left	86±24	68±28	**0.007**
Heel rises	(n)	right	61±44	32±38	**0.018**
		left	61±45	31±42	**0.010**
Functional reach	(cm)		84±21	71±25	**0.042**

Mean ± standard deviation.

Significant group differences for handgrip strength in both hands, heel rises in both legs and functional reach as well as for age and comorbidity were found in the subsequent univariate analyses including each physical performance measure, age, sex and comorbidity (figure 1).

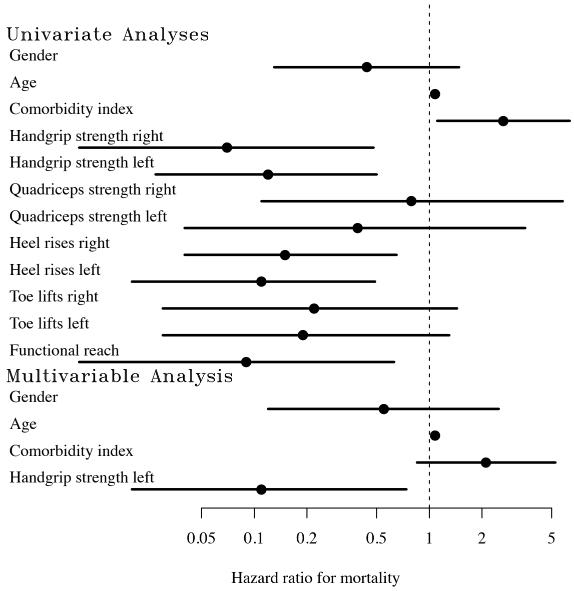

Figure 1. Univariate analyses for all measures and multivariable analyses for handgrip strength left
Reference values = dotted line for: sex = male, age = 65 years, comorbidity index = 0-1 comorbidities, handgrip strength, quadriceps strength and functional reach = mean normal, heel rises = 25, toe lifts = 20; physical performance measures expressed as 1 unit increase.

A reduction of handgrip strength left by 50% was associated with about a 3-fold increase in mortality (figure 2).

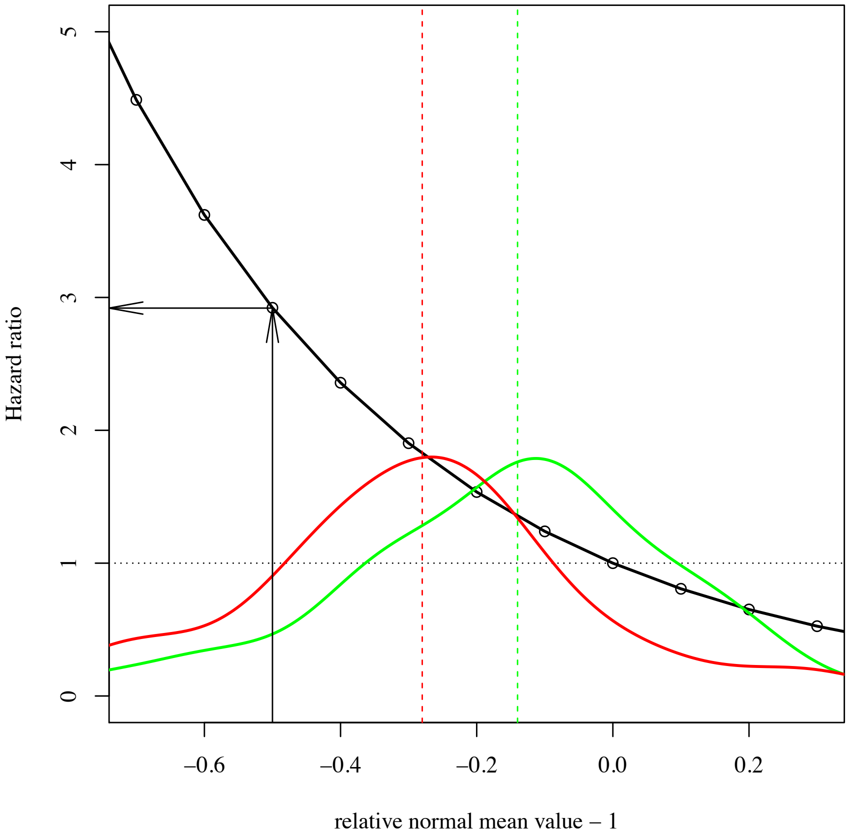

Figure 2. Relationship between loss of handgrip strength left and survival
Relative decrease in handgrip strength left, measured as the relative normal mean value -1, in relation to the relative risk of death.
Solid black line = hazard ratio; dotted green line = median handgrip strength left in survivors; solid green line = distribution of handgrip strength left in survivors; dotted red line = median handgrip strength left in deceased patients; solid red line = distribution of handgrip strength left in deceased patients; Arrows indicate hazard ratio for 50% reduction in handgrip strength left.

Study II – physical performance and mGFR in NDD-CKD

After 101 patients (40 women and 61 men, mean age: 67±13 years, mean mGFR: 22±8 ml/min/1,73m^2) were included in RENEXC there were enough baseline data available for analysis. General clinical characteristics are presented in table 4 and physical performance measures in table 5.

Table 4.
General clinical characteristics – study II

General clinical characteristics	Units	All
Age	years	67±13
BMI	kg/m^2	28.1±5.5
mGFR	mL/min/1.73m^2	22±8
P-Creatinine	μmol/L	262±98
P-Urea	mmol/L	16±5
C-reactive protein	mg/L	1.5 – 3.0 - 5.8
P-Albumin	g/L	37±3
Hemoglobin	g/L	128±13
Base excess	μmol/L	-3.1 – (-1.4) – 0.1
P-Potassium	mmol/L	4.2±0.5
P-Calcium	mmol/L	2.3±0.1
P-Phosphate	mmol/L	1.2±0.3
Parathyroid hormone	pmol/L	9 – 12 - 18
U-ACR	mg/mmol	4 – 35 – 126
24-hour ambulatory blood pressure, day	mmHg	134/77±15/11
24-hour ambulatory blood pressure, night	mmHg	120/65±23/13

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; BMI = body mass index; mGFR = measured glomerular filtration rate = iohexol clearance; P = plasma; U-ACR = urine-albumin-creatinine-ratio.

Physical performance measures of the whole population are presented in table 5. Balance capacity can be regarded as relatively well preserved in the study population with 96 % of the expected norm in functional reach and an average score of 52 of a maximum of 56 in the Berg balance scale. The lowest values were measured for muscular endurance in the distal leg muscles with 36 % in the right- and 32 % in the left toe lift measurement in relation to the expected norm. These measurements are followed in ascending order with the results in heel rises, climbing capacity, chair rises, walking capacity and finally muscle strength in the quadriceps muscle. Strength in the quadriceps muscle was also relatively well preserved with about 90 % of the expected norm. Nevertheless, a general loss of physical performance had started, was most pronounced in the distal leg muscles and less in the quadriceps muscle and balance capacity.

Table 5.
Physical performance at baseline – Study II – RENEXC substudy

Physical performance		Units		Observed values	Relative values
Overall endurance					
	6-minute walk test	m		384±140	76±24
	Stair climbing	n		4–7–12	NA
Muscular endurance / fatigability					
	Proximal leg muscles				
	30 seconds sit to stand	n		11±6	68±32
	Distal leg muscles				
	Heel rises	n	right	0-7-20	0-26-80
		n	left	0-7-20	0-28-80
	Toe lifts	n	right	0-0-12	0-10-75
		n	left	0-11-10	0-5-50
Neuromuscular function / strength					
	Lower extremity				
	Quadriceps strength	kg*m	right	11.4±4.4	91±27
		kg*m	left	11.3±4.5	90±26
	Upper extremity				
	Handgrip strength	kg	right	31±11	85±20
		kg	left	29±11	84±21
Balance					
	Functional reach	cm		33±9	96±25
	Berg balance scale	score		52±7	NA
Fine motor skills					
	Moberg's picking up test				
	with open eyes	sec	right	8.4±2.2	NA
		sec	left	8.6±2.2	NA
	with closed eyes	sec	right	23.7±16.0	NA
		sec	left	23.4±8.7	NA

Mean ± standard deviation, 1^{st} – 2^{nd} – 3^{rd} quartiles; NA = not available; relative values are presented in % and in relation to the expected norm.

The multivariable regression analyses showed significant relationships between measured GFR as the independent variable and 6-minute walk test (p=0.04), isometric quadriceps strength left leg (p=0.04), functional reach (p=0.02) and Moberg's picking up test with the left hand and open eyes (p=0.01). None of the other measured physical performance measures showed statistically significant associations with mGFR.

In practical terms a decrease of 10 ml/min/1.73m^2 in mGFR corresponded with 35m shorter walking distance and 10% weaker quadriceps strength.

Studies III and IV – RENEXC – general characteristics

After 217 patients had been screened, 151 were included (53 women, 98 men; mean age: 66±14 years; mean mGFR 22±8 ml/min/1.73m^2).

The majority of the patients were staged at CKD 4 comprising 62 % (n=93), CKD 5 with 27% (n=41) and CKD 3 with 10 % (n=15).

The general clinical characteristics and causes of kidney disease are presented for the whole RENEXC study group of 151 participants at baseline in table 6. (Studies III and IV)

Table 6.
General clinical characteristics of all RENEXC participants at baseline – (Studies III and IV)

General clinical characteristics	Units	All at baseline
Age	years	66±14
BMI	kg/m^2	28±5
mGFR	mL/min/1.73m^2	22±8
P-Creatinine	µmol/L	254±104
P-Urea	mmol/L	16±5
C-reactive protein	mg/L	1.5–3.0-6.1
P-Albumin	g/L	37±4
Hemoglobin	g/L	127±13
Base excess	µmol/L	-3.2–(-1.2)–0.1
P-Potassium	mmol/L	4.2±0.5
P-Calcium	mmol/L	2.3±0.1
P-Phosphate	mmol/L	1.2±0.3
Parathyroid hormone	pmol/L	9–12-18
U-ACR	mg/mol	4–35–126
24-hour ambulatory blood pressure, day	mmHg	134/78±15/11
24-hour ambulatory blood pressure, night	mmHg	120/67±21/12
Causes of Kidney Disease	N= 151	Relative
Hypertension	62	41%
Diabetes Mellitus	24	16%
Glomerulonephritis	23	15%
Interstitial Nephritis	22	15%
Polycystic Kidney Disease	9	6%
Others	11	7%

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; BMI = body mass index; mGFR = measured glomerular filtration rate = iohexol clearance; P = plasma; U-ACR = urine-albumin-creatinine-ratio.

The results of the different physical performance measures are presented for the whole RENEXC study group of 151 participants at baseline in table 7. (Studies III and IV)

Table 7.
Physical performance of all RENEXC participants at baseline (Studies III and IV)

		Units		Observed values	Relative values
Overall endurance					
	6-minute walk test	m		402±137	78±23
	Stair climbing	n		4–7–13	NA
Muscular endurance / fatigability					
	Proximal leg muscles				
	30 seconds sit to stand	n		11±6	72±36
	Distal leg muscles				
	Heel rises	n	right	0-7-20	0-28-80
		n	left	0-7-21	0-28-80
	Toe lifts	n	right	0-2-15	0-10-75
		n	left	0-2-11	0-10-53
Neuromuscular function / strength					
	Lower extremity				
	Quadriceps strength	kg*m	right	11.4±4.1	91±26
		kg*m	left	11.3±4.2	90±26
	Upper extremity				
	Handgrip strength	kg	right	32±10	84±21
		kg	left	28±11	84±23
Balance					
	Functional reach	cm		33±9	97±24
	Berg balance scale	score		51±8	NA
Fine motor skills					
	Moberg's picking up test				
	with open eyes	sec	right	8.3±2.1	NA
		sec	left	8.5±2.4	NA
	with closed eyes	sec	right	23.0±13.9	NA
		sec	left	23.2±8.9	NA

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; NA = not available; relative values are presented in % and in relation to the expected norm.

In addition to the RENEXC related structured examinations, assessments and exercise training programs, all participants were followed up at the outpatient clinic according to the established routines at the department. Each patient received usual standard nephrology care by the multiprofessional team under the direction of each patient's nephrologist.

Three patients dropped out shortly after randomization and before baseline assessment due to bone fracture, terminal illness and recurring retinal haemorrhage.

The CONSORT flow diagram (figure 3) shows that, during 12 months of the intervention period, 23 patients discontinued in the strength group and 16 in the balance group. Three patients died, for reasons unrelated to the study. Other reasons for the lack of data after 4, 8 and 12 months were concomitant illness, travel, moving to another town or no motivation to continue.

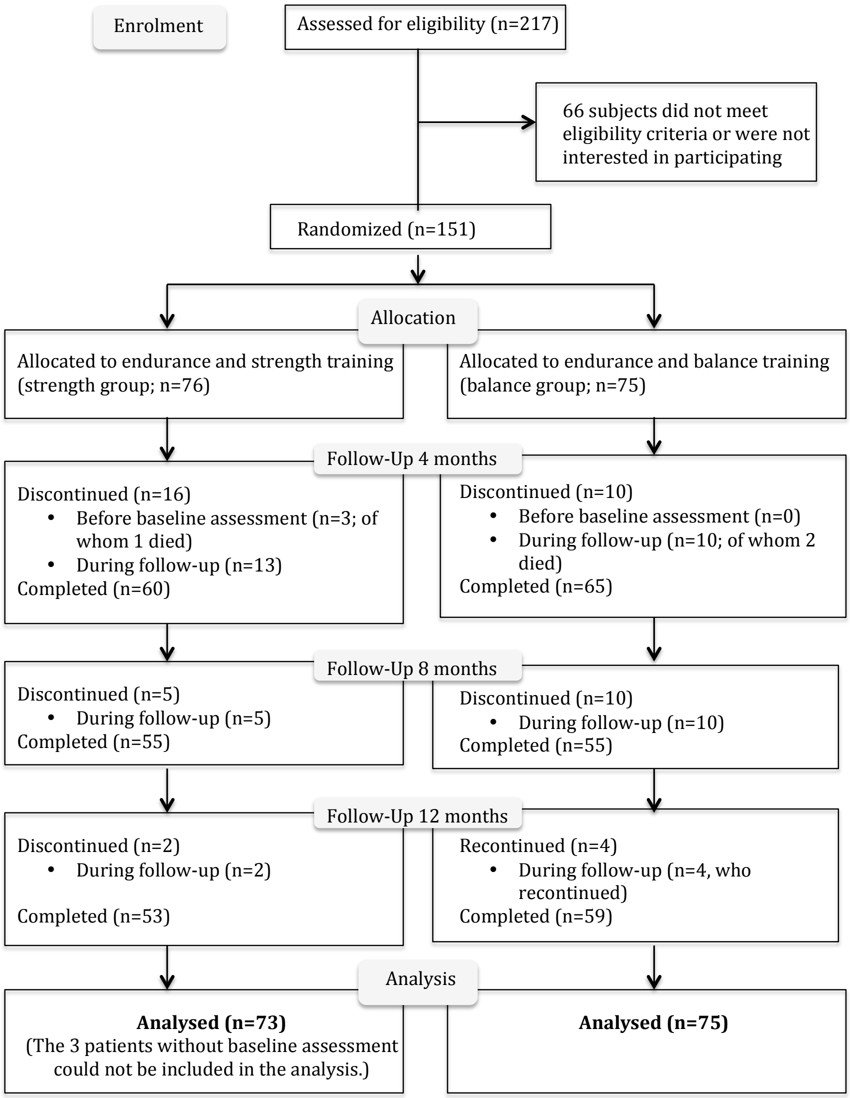

Figure 3. CONSORT flow diagram - RENEXC

Study III – physical performance after 4 months of exercise training

The observed values and estimated effects after 4 months of exercise training are presented in table 8 for the strength group and table 9 for the balance group. A graphical overview is given in figures 4, 5 and 6.
Apart from a statistically significant greater increase in quadriceps strength right in the strength group (P<0.001), there were no statistically significant differences between groups.

83 % (n=125) of the included patients completed the 4 months intervention period. The strength group achieved on average 98 % and the balance group 107 % of the prescribed 150 minutes of exercise training time per week.

Table 8.
Effects after 4 months of strength- and endurance exercise training on physical performance (Study III)

Physical performance		Units		Observed valuea	Est. effects	p
Overall endurance						
	6-minute walk test	m		400±149	14 [0–28]	**0.05**
	Stair climbing	n		5–8–14	2 [0-3]	**0.02**
Muscular endurance/fatigability						
	Proximal leg muscles					
	30 seconds sit to stand	n		11±7	1 [0-1]	**0.007**
	Distal leg muscles					
	Heel rises	n	right	0-11-22	2 [0-4]	**0.04**
		n	left	0-13-27	3 [0-5]	**0.01**
	Toe lifts	n	right	0-4-19	2 [1-4]	**0.01**
		n	left	0-4-14	2 [0-4]	0.06
Neuromuscular function/strength						
	Lower extremity					
	Quadriceps strength	kg*m	right	12.8±4.2	1.3 [0.8-1.7]	**<0.001**
		kg*m	left	12.6±4.7	0.9 [0.3-1.4]	**0.001**
	Upper extremity					
	Handgrip strength	kg	right	33±9	0 [-1-1]	0.9
		kg	left	30±9	0 [-1-1]	0.7
Balance						
	Functional reach	cm		33±9	1 [0-3]	0.09
	Berg balance scale	score		51±9	1 [0-1]	0.7
Fine motor skills						
	Moberg's picking up test					
	with open eyes	sec	Right	8.3±2.2	-0.4 [-0.7-0]	0.08
		sec	Left	8.4±2.6	-0.3 [-0.7-0]	0.07
	with closed eyes	sec	Right	21.4±8.7	-3.1 [-5.6-(-0.3)]	**0.03**
		sec	Left	22.0±8.5	-1.5 [-2.9-(-0.1)]	**0.03**

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; est. effects = estimated effects by mixed model analysis; NA = not available; [..–..] = 95% confidence interval.

Both the strength- and balance group improved or stabilized all measures of physical performance without any deterioration in any of the tests. Significant improvements in both groups could be found for measures of muscular endurance, muscular strength and fine motor skills. Furthermore, the strength group showed improvement both in measures of overall endurance, i.e. walking and stair climbing capacity, as well as in muscular endurance in the proximal leg muscles measured as 30-STS.

Measures of handgrip strength as well as functional reach were unchanged after 4 months of regular strength- or balance exercise training combined with endurance.

Table 9.
Effects after 4 months of balance- and endurance exercise training on physical performance (Study III)

Physical performance		Units		Observed values	Est. effects	p
Overall endurance						
	6-minute walk test	m		445±147	11 [-3–25]	0.1
	Stair climbing	n		5–7–15	0 [-1-2]	0.9
Muscular endurance/fatigability						
	Proximal leg muscles					
	30 seconds sit to stand	n		13±6	1 [0-1]	0.08
	Distal leg muscles					
	Heel rises	n	right	2-15-27	3 [1-5]	**<0.001**
		n	left	0-11-28	3 [1-5]	**0.004**
	Toe lifts	n	right	0-7-19	1 [0-3]	0.1
		n	left	0-5-18	2 [0-3]	0.08
Neuromuscular function/strength						
	Lower extremity					
	Quadriceps strength	kg*m	right	11.7±4.3	0.0 [-0.4-0.5]	0.9
		kg*m	left	11.9±4.5	0.7 [0.2-1.2]	**0.003**
	Upper extremity					
	Handgrip strength	kg	right	32±12	0 [-1-1]	0.9
		kg	left	29±11	0 [-1-1]	0.8
Balance						
	Functional reach	cm		35±8	1 [-1-2]	0.3
	Berg balance scale	score		53±5	1 [0-1]	**0.04**
Fine motor skills						
	Moberg's picking up test					
	with open eyes	sec	right	7.8±2.0	-0.1 [-0.5-0.3]	0.5
		sec	left	7.8±1.9	-0.4 [-0.7-(-0.1)]	**0.02**
	with closed eyes	sec	right	20.8±7.7	-0.8 [-3.5-(-1.9)]	0.6
		sec	left	20.7±8.2	-2.0 [-3.4-(-0.7)]	**0.003**

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; est. effects = estimated effects by mixed model analysis; NA = not available; [..–..] = 95% confidence interval.

Study IV – physical performance and kidney function after 12 months of exercise training

After all participants had finished the assessment after 12 months of intervention in May 2017, the whole period could be analysed. The observed values and estimated effects after 12 months of strength and endurance exercise training are presented in table 10 (strength group) and the effects on physical performance after 12 months balance and endurance exercise training in table 11 (balance group) as well as in a graphical overview in figures 4, 5 and 6.

Effects on overall endurance, muscular endurance, muscular strength, balance and fine motor skills are characterized by further improvement or maintenance in comparison with the effects after 4 months of intervention.

Table 10.
Effects after 12 months strength- and endurance exercise training on physical performance (Study IV)

Physical performance		Units		Observed values	Est. effects	p
Overall endurance						
	6-minute walk test	m		450±127	31 [16–46]	**<0.001**
	Stair climbing	n		5–10–23	6 [3-8]	**<0.001**
Muscular endurance/fatigability						
	Proximal leg muscles					
	30 seconds sit to stand	n		13±7	1 [1-2]	**<0.001**
	Distal leg muscles					
	Heel rises	n	right	5-19-30	7 [4-9]	**<0.001**
		n	left	1-17-27	6 [4-8]	**<0.001**
	Toe lifts	n	right	0-9-25	4 [2-6]	**0.001**
		n	left	0-4-20	3 [1-5]	**0.003**
Neuromuscular function/strength						
	Lower extremity					
	Quadriceps strength	kg*m	right	13.3±4.4	1.2 [0.7-1.7]	**<0.001**
		kg*m	left	13.1±4.9	0.8 [0.3-1.4]	**0.003**
	Upper extremity					
	Handgrip strength	kg	right	33±10	0 [-1-1]	0.5
		kg	left	31±10	1 [0-2]	0.3
Balance						
	Functional reach	cm		36±7	2 [1-4]	**0.003**
	Berg balance scale	score		52±9	0 [-1-1]	0.8
Fine motor skills						
	Moberg's picking up test					
	with open eyes	sec	right	7.8±2.0	-0.7 [-1.0-(-0.3)]	**<0.001**
		sec	left	8.0±2.3	-0.4 [-0.7-(-0.1)]	**0.01**
	with closed eyes	sec	right	19.5±6.7	-4.0 [-6.4-(-1.7)]	**<0.001**
		sec	left	20.9±7.2	-1.6 [-3.3-(-0.0)]	**0.05**

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; est. effects = estimated effects by mixed model analysis; NA = not available; [..–..] = 95% confidence interval.

The improvement in physical performance achieved after 4 months of strength- and endurance exercise training was sustained throughout the 12 months intervention period.

The balance group achieved significant improvements in general after 12 months of exercise training.

Nevertheless, after 12 months of regular and self-administered exercise training both groups achieved comparable effects on physical performance, regardless of training modality. There were, however, no statistically significant effects between the strength- and balance group after 12 months of exercise training. Albeit, the combination of strength- and endurance exercise training appeared to be more effective as significant effects appeared earlier than in the balance- and endurance exercise training.

Table 11.
Effects after 12 months of balance- and endurance exercise training on physical performance (Study IV)

Physical performance		Units		Observed values	Est. effects	p
Overall endurance						
	6-minute walk test	m		469±133	24 [10–37]	**<0.001**
	Stair climbing	n		6–9–26	5 [3-7]	**<0.001**
Muscular endurance/fatigability						
	Proximal leg muscles					
	30 seconds sit to stand	n		13±8	1 [0-2]	**0.001**
	Distal leg muscles					
	Heel rises	n	right	3-20-31	8 [5-10]	**<0.001**
		n	left	1-17-27	6 [4-9]	**<0.001**
	Toe lifts	n	right	0-10-25	6 [3-8]	**<0.001**
		n	left	0-7-25	4 [3-6]	**<0.001**
Neuromuscular function/strength						
	Lower extremity					
	Quadriceps strength	kg*m	right	12.1±4.3	0.6 [0.1-1.1]	**0.01**
		kg*m	left	11.9±4.4	0.9 [0.3-1.4]	**0.001**
	Upper extremity					
	Handgrip strength	kg	right	32±12	0 [-1-1]	0.3
		kg	left	29±11	0 [-1-1]	0.7
Balance						
	Functional reach	cm		36±8	2 [0-3]	**0.008**
	Berg balance scale	score		52±8	0 [-1-1]	0.9
Fine motor skills						
	Moberg's picking up test					
	with open eyes	sec	right	7.7±2.0	-0.3 [-0.6-0.0]	0.06
		sec	left	8.0±1.8	-0.3 [-0.6-0.0]	**0.05**
	with closed eyes	sec	right	19.4±6.2	-2.4 [-4.7-(-0.2)]	**0.04**
		sec	left	21.7±9.3	-1.3 [-2.8-0.3]	0.1

Mean ± standard deviation, 1st – 2nd – 3rd quartiles; est. effects = estimated effects by mixed model analysis; NA = not available; [..–..] = 95% confidence interval.

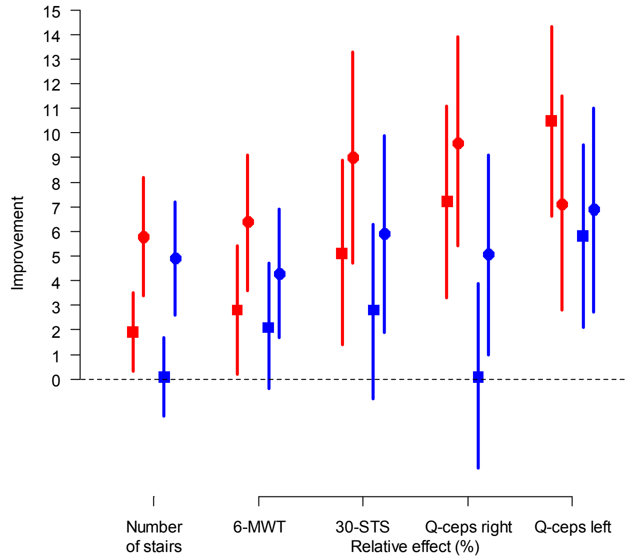

Figure 4. Effects after 4 and 12 months on stair climbing and walking capacity, chair rises within 30 seconds and isometric quadriceps strength (Studies III and IV)
Improvements in stair climbing capacity - presented as numbers of flights of stairs. Improvements in walking capacity measured with the 6-MWT, chair rises within 30 second with the 30-STS and isometric quadriceps strength (Q-ceps) in the right and the left leg - presented in relation to the expected norm as relative effects in %;
Red = strength group; Blue = balance group; square (■) = 4 months, circle (●) = 12 months.

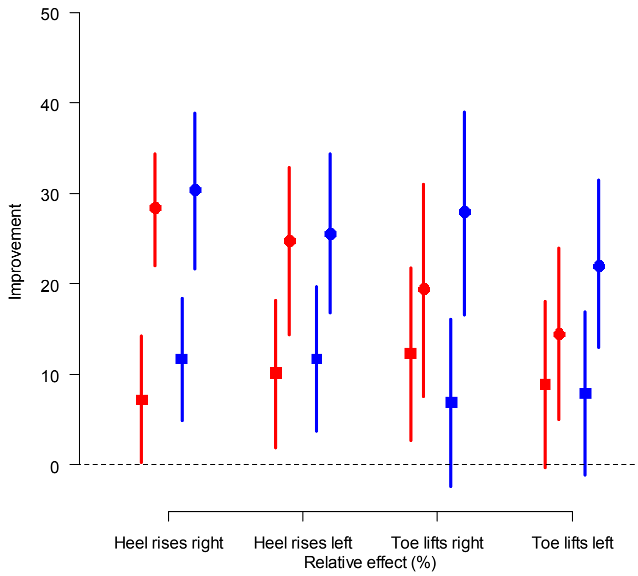

Figure 5. Effects after 4 and 12 months on muscular endurance in the distal legs (Studies III and IV)
Improvements in muscular endurance in the distal leg muscles are presented for heel rises right and left and for toe lifts right and left as relative effects in %, related to the expected norm;
Red = strength group; Blue = balance group; square (■) = 4 months, circle (●) = 12 months.

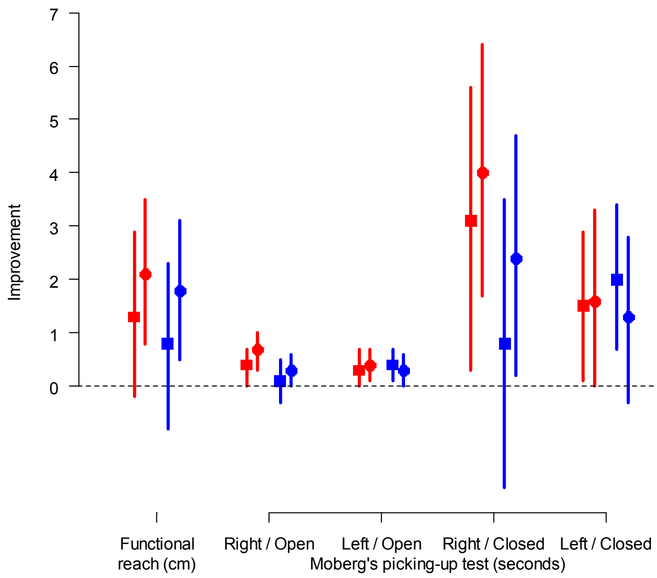

Figure 6. Effects after 4 and 12 months on balance and fine motor skills (Studies III and IV)
Improvements in absolute values on balance measured as functional reach in cm and on fine motor skills with Moberg's picking up test in the right and the left hand with open and closed eyes, respectively in seconds; Red = strength group; Blue = balance group; square (■) = 4 months, circle (●) = 12 months.

Kidney Function

Kidney function was measured with iohexol clearance as mGFR at baseline and after 12 months at the end of the intervention period for both the strength- and the balance group (table 12 and 13). The baseline values as well as the decrease in mGFR were similar in both groups. There was no statistically significant group difference.

Albuminuria showed a decrease in U-ACR during the intervention period in both groups. The decrease of about 33 % was statistically significant in the strength group after 12 months exercise training. The difference between groups was statistically significant (p=0.02).

Table 12.
Kidney function after 12 months of strength- and endurance exercise training (Study IV)

	Months	Observed values	Mean estimated effects	P
mGFR (mL/min/1.73m^2)				
	0	22.6±8.7		
	12	21.9±9.7	-1.8 [-3.2-(-0.4)]	**0.01**
U-ACR (mg/mmol)				
	0	98±140		
	12	64±98	-33 [-50 – (-16)]	**<0.001**

Mean ± standard deviation; [..-..] = 95% confidence interval; mGFR = measured glomerular filtration rate = iohexol clearance; U-ACR = urin-albumin-creatinine-ratio.

Table 13.
Kidney function after 12 months of balance and endurance exercise training (Study IV)

	Months	Observed values	Mean estimated effects	P
mGFR (mL/min/1.73m^2)				
	0	22.4±7.7		
	12	21.2±7.8	-1.8 [-3.1-(-0.4)]	**0.01**
U-ACR (mg/mmol)				
	0	84±114		
	12	71±99	-5 [-21-11]	0.5

Mean ± standard deviation; [..-..] = 95% confidence interval; mGFR = measured glomerular filtration rate = iohexol clearance; U-ACR = urin-albumin-creatinine-ratio.

Discussion

It was possible to perform a survival analysis, in our retrospective study, as all patients starting chronic dialysis treatment were registered in the Swedish Renal Registry. The physical performance assessment protocols, in patients who were approaching or had just initiated chronic dialysis treatment, were another prerequisite for the study. Despite the retrospective nature of the study and the limited number of patients (n=134) with evaluable physical performance measures, the data set was unique and collected in everyday clinical routine. The results for stair climbing and Moberg's picking up test did not consistently permit an unambiguous characterization, so we chose not to include those measures in our study. Both the alive and the deceased group had similar clinical characteristics, except for older age and slightly higher comorbidity in the deceased group.

In Lund, the comprehensive test battery for physical performance in conjunction with starting maintenance dialysis was feasible in clinical routine. Subsequently, the test battery was extended to patients with NDD-CKD followed at the outpatient clinic in Lund. The measurements enabled early detection of impairments to physical performance as well as timely recommendations of exercise training. RENEXC was designed to be an integrated part of the established clinical structures at the department. The test battery was extended with three widely used tests (6-MWT, 30-STS and Berg balance scale). A precise prescription of 150 minutes of exercise training per week, individualised and self-administered was added to routine care as part of RENEXC. A structured and controlled follow-up were prerequisites for scientific evaluation. All prevalent and incident patients, with NDD-CKD, treated at the outpatient clinic in Lund, were invited to join, irrespective of age and comorbidity, and after consideration of the exclusion criteria. Thus, a sample of patients who were representative of a population with NDD-CKD could be obtained.

Overall endurance

In an earlier observational study, walking distance, measured with the 6-minute walk test in patients with CKD 2-4, was important for survival. The authors reported a better survival rate if the distance walked was longer than 350 m, or expressed differently: there was a 2.82-fold increased risk for death when the walking distance was less than 350m.[37] The recently published multicentre RCT

EXCITE, in patients with DD-CKD, showed an 11 % decrease in risk of mortality for each 20 m longer walking distance in a secondary analysis.[184]

In patients with NDD-CKD in RENEXC, we found a reduction in overall endurance, measured with the 6-minute walk test and the stair climbing test. Patients in RENEXC reached a walking distance of 86% of the expected norm and 58% of the cut of value of 12 flights of stairs in the stair climbing test. Furthermore, the decline in walking distance was related to the decline in mGFR. We found that a 35 m shorter walking distance corresponded to a decline of 10 ml/min/1.73m^2 in mGFR. A similar relationship was reported between maximal exercise capacity, measured as W_{max} on a cycle ergometer, and GFR in patients with NDD-CKD [46].

Strength- and endurance exercise training improved both in the 6-MWT and stair climbing test after 4 months und further during the 12 months of intervention. In contrast, the balance group, showed unchanged levels after 4 months and improvement after 12 months. To date, the largest exercise training RCT in NDD-CKD patients comprised 36 exercising patients and 36 controls. The intervention, consisting of strength- and endurance training for 12 months, resulted in increased performance in the 6-MWT and the get up and go test as well as in VO_{2peak}.[141, 147] Similar results on VO_{2peak} were shown with strength- and endurance exercise training three times per week for 12 months in a smaller study group consisting of 10 exercising patients and 10 controls with CKD 3-4. [140] Another study reported an increase in VO_{2peak} after endurance training for 11 months in patients with CKD 2-4.[173] The multicentre study, EXCITE, was conducted in patients with DD-CKD during a period of 6 months and was based on a simple home based walking program.[102] Walking capacity was improved, measured with the 6-MWT, from 328 m to 367 m in the exercise group.[102]

In the patients in RENEXC, stair climbing capacity was reduced to a median number of 7 flights of steps. The strength- and endurance training improved climbing capacity already after 4 months and maintained this improvement after 12 months. The balance group showed an improvement in stair climbing after 12 months of exercise training. Aoike et al. used the 2 minutes step test (maximal number of steps in stationary walking) in a RCT investigating endurance training during 12 weeks in patients with NDD-CKD. They found an increase in number of steps from 180 to 219, but no effect on VO_{2max}.[103] Stair climbing tests are often timed or combined with walking tests and seem to show a higher correlation with VO_{2max}, as shown by Mercer et al. with the WALK test in patients with DD-CKD.[84] In one study, patients with DD-CKD trained strength and endurance for 20 to 30 minutes twice per week for 5 months without any changes in a stair climbing test within 2 minutes. However, they improved their aerobic capacity and the time it took to perform 10 squats.[159]

Muscular endurance

Distal leg muscles are tested by heel rises and toe lifts. In our retrospective study, the ability to perform heel rises was better in the alive group and was associated with better survival. Both the alive- and the deceased group performed extremely low numbers of toe lifts, making it difficult to detect any difference. Both measures were reduced in the NDD-CKD patients in RENEXC, but the impairment was most pronounced for toe lifts, which were reduced to the level measured in the alive group of the retrospective study. We did not find an association with loss of mGFR.

Both the strength- and the balance group showed an improvement in heel rises after 4 months and 12 months. Toe lifts improved in the strength group after 4 months and was sustained after 12 months. The balance group needed 12 months to achieve an improvement. A recently published study in older adults showed improved endurance in the calf muscle, tested by heel rises, after a balance training program twice a week for 5 weeks. They also reported a low risk of falls if the subjects were able to perform at least 10 unilateral heel rises [185].

Muscular strength

Muscular strength in the largest muscle of the body, quadriceps femoris, was similar in both the alive- and the deceased groups in our retrospective study. Similar results, with a relatively well preserved quadriceps strength, was confirmed in the baseline data analysis of the RENEXC population (studies II, III and IV). It is noteworthy, that strength in the quadriceps muscle was better preserved compared with the other measures of physical performance. The quadriceps muscle seems to have a capacity to sustain strength at a level of about 90 % of the expected norm during CKD stages 3a to 5. However, there was a slight decrease, which corresponded to the decline in GFR. After taking age, sex and comorbidity into account, the loss of 10 % strength in the left quadriceps muscle was significantly associated with a decline in mGFR of 10 ml/min/1.73m^2. Our results for quadriceps strength are in accordance with earlier studies in elderly patients with NDD-CKD.[88] Moreover, they are consistent with the results from muscle biopsies in men with NDD-CKD, which showed no signs of muscle atrophy.[186] However, muscle atrophy and loss of muscular strength is considerable in patients with DD-CKD.[89, 187, 188] Patients with DD-CKD and severely decreased muscular strength in the thighs showed a 2.7 fold higher risk of death compared with patients who had a better thigh strength, after sex, age, comorbidity, BMI, time on hemodialysis, markers of nutrition and inflammation were taken into account.[189]

This tendency to lose quadriceps strength was counteracted by both strength and balance training in RENEXC, with a more pronounced effect already after 4 months in the strength group. However, after 12 months of exercise training both groups showed a similar and significant improvement. In earlier RCTs patients with NDD-CKD showed significant improvement in quadriceps strength after 8 and 12 weeks of strength training.[86, 149, 190] In a previous study, patients with NDD-CKD improved quadriceps strength after 4 months of endurance exercise training. In that study the duration of the exercise training was increased from 30 to 60 minutes per session and the exertion level was maintained at 70%.[161] Elderly patients with NDD-CKD, who trained muscular strength and endurance in the thighs, showed a similar improvement in strength and endurance in the thighs as their healthy elderly counterparts.[87]

Patients with DD-CKD showed improved quadriceps strength after three months of combined strength and endurance exercise training in an earlier RCT.[88] Another RCT, with only endurance exercise training, showed improved quadriceps strength in patients with DD-CKD after twenty weeks.[155] In other previous RCTs, in patients with DD-CKD, 3 to 6 months of only strength training improved quadriceps strength too.[145, 154, 156]

We used handgrip strength as the isometric measure of strength in the upper extremity. The alive group in the retrospective study and the patients in RENEXC at baseline (studies II, III and IV) all had a handgrip strength of about 85 % compared with the expected norm. These results are in accordance with other reports.[95, 96] The deceased group in study I only reached about 70 % of the expected norm. Furthermore, we found that a 50% reduction in handgrip strength in the left hand, after adjustment for age, sex and comorbidity, was significantly associated with an almost three fold increase in mortality. Our findings emphasize the importance of handgrip strength in patients with CKD and are in line with earlier studies. Others have previously reported associations between reduced handgrip strength and a faster progression towards end stage renal disease, as well as a higher mortality rate in patients with NDD-CKD and in men with DD-CKD.[95, 99] Loss of handgrip strength seems to be common in patients with CKD. Further loss seems to be an important marker for increased mortality.

In RENEXC, after 12 months of exercise training, handgrip strength was unchanged in both groups. It is of interest, that handgrip strength, in the patients in RENEXC, was at the same level as in the alive group in the retrospective study, which we found to be a survival advantage. Previous RCTs, investigating the effects of regular exercise training, also assessed handgrip strength, but did not find an exercise training effect. This was reported in patients with NDD-CKD after 12 months of combined strength- and endurance exercise training as well as in patients with DD-CKD after three months of strength exercise training.[141, 156] This leads one to speculate how handgrip strength is sustained in patients with CKD. It is possible that a further decrease in handgrip strength was counteracted by the exercise training. The mechanism might not be a direct effect of the exercise training, but could be due to anti-catabolic and anti-inflammatory effects attributed to exercise training.

Handgrip strength is also used in the context of assessing nutritional status, evaluating the effects of inflammation, subsequent muscle weakness and sarcopenia and its association with morbidity and mortality.[85, 93-95] Muscle weakness is one of the 5 dimensions when assessing frailty. It is defined as a decrease in handgrip strength of at least 20% below the expected norm. The deceased group, in our retrospective study, could definitely be categorized as pre-frail, maybe even frail, but due to lack of further information we can only speculate. To summarize, handgrip strength does not seem to be suitable as a direct measure of the effects of regular exercise training. Nevertheless, handgrip strength should be assessed and used to diagnose sarcopenia and frailty and could be regarded as an indirect measure of long term exercise training.

Balance

Dynamic balance, measured with the functional reach test, was part of the ordinary physical performance test battery used in Lund before RENEXC and was evaluated in the survival analysis in our retrospective study. The deceased group had a significantly lower level compared with the expected norm, with an average of about 71%, while the alive group attained about 84 % of the expected norm.

In the RENEXC baseline analyses (studies II, III, IV), functional reach was on average 96 % of the expected norm with similar results in the Berg balance scale with 92 % of the expected norm. After adjustment for age, sex and comorbidity, a decrease in functional reach was significantly related to a decline in mGFR. This finding is corroborated by Reese et al., when investigating frailty and CKD. They found an association between the decline in eGFR and the results in the short physical performance battery (SPPB), which included a measurement of balance.[126] Functional reach showed a slightly higher level in relative terms than quadriceps strength, when comparing test results from the retrospective survival analysis with the RENEXC baseline analyses (studies II, III, IV). Thus, indirectly confirming a further loss of balance capacity as GFR declines. This is in accordance with earlier reports of an increase in frailty as GFR declines. Moreover, a previous study reporting a high risk of falls in patients with DD-CKD also supports our findings.[126, 191] In another baseline analysis of RENEXC data, we found significant associations between functional reach and quadriceps strength as well as with lean mass in the legs measured by DEXA, on the other hand, Berg balance scale was associated with lean mass in the trunk.[192]

Although, the patients with NDD-CKD in RENEXC had a slight reduction of balance capacity at baseline, they normalized their balance capacity after 12 months of exercise training. The strength group showed a significant improvement already after 4 months and the balance group after 8 months of exercise training. Thus, we found that a slight decrease in balance capacity, measured by functional reach, was counteracted by regular and self-administered exercise training, consisting of either strength- or balance- both combined with endurance exercise training. The strength group attained an improvement already after 4 months, while the balance group required 8 months to achieve a similar effect. In contrast to the functional reach test, the Berg balance scale, which comprises 14 different tests, did not detect any changes in balance capacity after exercise training. This test is considerably more time-consuming and, in consequence, less suitable than the functional reach test in patients with NDD-CKD. Balance capacity was relatively well preserved in the RENEXC population. Most patients reached a level of about 50 to 52 of a maximum of 56 points in the Berg balance scale. Of the 14 tests in the Berg balance scale, standing on one leg determined the final results. If one wishes to use an easy to perform static balance test in patients with NDD-CKD, then standing on one leg test would be a good choice.

Fine motor skills

Moberg's picking up test measures the time needed to pick up 10 different items with open and closed eyes, with the right and the left hand, respectively. In the baseline analysis in RENEXC, it took about three times longer for the patients with NDD-CKD to pick up the items with closed eyes compared with open eyes, which is in accordance with earlier reports.[174, 183] We found that, after adjusting for age, sex and comorbidity, the picking up time with the left hand and open eyes was significantly associated with a decline in mGFR. Diminished fine motor skills have been described in children with NDD-CKD.[193] Hence, it is reasonable to believe, that an impairment in fine motor skills can be detected by Moberg's picking up test in patients with NDD-CKD.

One can reflect over, why only the test with open eyes and the left hand was significantly associated with a decline in mGFR in the RENEXC baseline analysis. One reason might be deterioration in the interplay between fine motor skills in the hands and the visual system. During the 12 months of exercise training, the picking up time did not become prolonged, neither in the right nor the left hands, nor with open or closed eyes. The strength group improved their results after 4 months in both hands with open and closed eyes and the effects were sustained after 8 and 12 months. The effects in the balance group were similar to the strength group in the left hand and with open eyes. The improvement in the left hand with closed eyes after 4 months of balance- and endurance exercise training disappeared after 8 months with no change after 12 months. The balance group improved picking up time for the right hand with closed eyes after 12 months. To summarize, strength- and endurance exercise training had more consistent and pronounced effects on fine motor skills compared with balance- and endurance exercise training. One possible explanation for the superiority of strength- and endurance exercise training might be that the strength group, already after 4 months, achieved significant effects on more measures of physical performance than the balance group, who in general required 12 months to obtain similar results.

Glomerular filtration rate

In RENEXC, the glomerular filtration rate was measured so as to eliminate creatinine and muscle mass related confounders and to obtain the most accurate results for GFR. GFR has also been measured in earlier RCTs investigating exercise training effects and GFR.[86, 139] Both the strength- and the balance groups showed a decline in mGFR with 1.8 ml/min/1.73m^2 after 12 months of exercise training. An observational study in patients with CKD stages 3 and 4 reported an annual decline in eGFR of 2.6 ml/min/1.73m^2 in the patients who reported physical activity of at least 150 minutes per week, compared with the sedentary patients who had an annual decline of 4.2 ml/min/1.73m^2.[194] Another study, reported that an increase from no physical activity to 30 minutes per week was associated with a 0.7 % slower decline in GFR, resulting in a one year later onset of end stage renal disease.[194] Other investigators reported that a decline of about 25 ml/min/1.73m^2 during 11 years of observation, which is on average 2.3 ml/min/1.73m^2 per year, was associated with self-reported low physical activity in middle-aged and older women.[195]

Experimental studies in uremic rats investigating the effects of daily exercise on GFR showed an improvement in GFR after 8 or 20 weeks.[168, 169] Low-intensity aerobic exercise training for 30 minutes twice a week showed an increase in GFR after 12 weeks.[170] Toyamao et al. reported an improvement in eGFR after regular exercise training for 12 and 20 weeks, respectively.[171, 172] The largest exercise training RCT until RENEXC, comprised 36 exercising patients with CKD stages 3 and 4 and 36 controls, showed no change in GFR in either group after the 12 months intervention period, which is unexpected and might be due to a sample of patients with very stable GFR.[141, 147] In RENEXC 12 months of regular exercise training presented, in comparison with observational studies, a slower decrease in GFR, measured with iohexol clearance. Increased or unchanged levels of GFR would have been unexpected. However, the relatively slow decline in GFR, during the 12 months of exercise training, might indicate a positive impact of regular exercise training on the rate of progression of CKD. One possible explanation could be anti-catabolic and anti-inflammatory effects of exercise training.[196, 197] In patients with DD-CKD combined strength- and endurance exercise training reduced CRP levels after 8 weeks.[167] In patients with NDD-CKD 12 weeks of strength exercise training decreased levels of both CRP and interleukin-6.[149]

Albuminuria

After 12 months of strength- and endurance exercise training albuminuria, measured as U-ACI, was decreased with 33% from 98 to 64 mg/mmol, while the balance group showed sustained levels. Previous observational studies showed associations between progress in albuminuria and loss of GFR as well as increased mortality, while a decrease in albuminuria was associated with a slower rate of progression of CKD.[5-7, 20-22, 198-200]

A decrease in albuminuria is considered to be a therapeutic target, when evaluating effects of renin-angiotensin-aldosterone system inhibitors, improved glucose control or anti-inflammatory agents.[201] Low intensity swimming exercise training, for at least 30 minutes twice a week, resulted in decreased proteinuria after an intervention period of 12 weeks.[170] A recently published observational study showed that a 4-fold increase in U-ACI was associated with a 3.08 higher risk, or conversely a 4-fold decrease in U-ACI was associated with a 0.34 lower risk of reaching end stage renal disease.[22] The significant decrease in albuminuria after 12 months of regular strength- and endurance exercise training, concurrent with a relatively slow decline in mGFR, is suggestive of the potential benefits of regular exercise training in patients with NDD-CKD. It is possible that regular exercise training might slow the decline in GFR and postpone reaching end stage renal disease as well as lowering the risk of mortality.

RENEXC – self-administered regular exercise training – adherence

RENEXC was designed as an RCT and integrated in clinical routine. In RENEXC there were wide inclusion criteria so as to comprise patients with NDD-CKD regardless of age, sex and comorbidity in order to achieve a representative sample of patients. After 4 months a total of 125 patients (83 %) had completed the intervention period and after 12 months a total of 112 patients (74 %) had completed. This level of completion was similar to the 79 % completers, reported in a pilot RCT with 10 exercising patients after 12 months.[140] The number of completers in RENEXC confirm the correctness of the underlying power calculation and assumptions with regard to the data volume available at the end of the intervention period and the expected loss to follow-up.

Howden reported adherence as the weekly amount of reported walking time in the, up to RENEXC, largest exercise training RCT in patients with NDD-CKD. Their study, which was also home based with an intervention period of 12 months, comprised 36 exercising patients. About 64% of the exercising patients reported 150 minutes or more walking time after 6 months and 57% after 12 months.[141] In Howden's study, the patients started with centre based exercise training for 2 months during which period their adherence was about 70 %. These results are similar to the results by Mustata et al., who reported an adherence of 80 % after 2 months centre based exercise training, with a decrease in adherence to 20 % after a switch to a home based exercise training program.[141, 202]

In RENEXC, 47 patients (62 %) in the strength group reported an average of 140 minutes per week of exercise training after the 12 months of intervention. In the balance group, 51 patients (68 %) reported on average 173 minutes per week of exercise training after the intervention period of 12 months. There are a number of factors that could contribute to the high adherence rate in RENEXC, such as the individualized exercise training program, high accessibility to the physiotherapist, the method of monitoring self-administration by using the Borg scale as well as the option to train at home or at a gym. The exercise training program in the multicentre EXCITE trial in patients with DD-CKD was based on low intensity home based walking exercise training.[102] At the end of the intervention period, after 6 months of exercise training, 76 of 150 included patients returned a correctly filled in training diary and 81 patients returned the metronome (used to monitor walking speed) for verification of the battery.[102] After 6 months, 104 of 151 patients completed the exercise intervention period, which was similar to the results in RENEXC with 112 of 151 patients completing, albeit after 12 months of intervention.[102]

To summarize, regular coaching by the dialysis staff as in the EXCITE trial or regular telephone contacts following up the exercise training prescription as in RENEXC and the study by Fitts et al. all resulted in better outcomes of self-administered exercise training in patients with both NDD-CKD and DD-CKD.[150]

Conclusions

The overall conclusion was, that impairment of physical performance seems to be prevalent early in the course of CKD and seems to decrease with the decline in GFR. Regular exercise training seems to counteract this trend effectively and seems to have positive effects on kidney function.

The specific conclusions were:

- Patients' survival after starting chronic dialysis treatment was associated with muscular strength in the distal arm muscles, muscular endurance in the distal leg muscles and balance, assessed prior to starting chronic dialysis treatment (**Study I**).
- The degree of decline in measured glomerular filtration rate was significantly associated with impaired measures of overall endurance, muscular strength in upper limbs, balance and fine motor skills in patients with a mGFR between 9 and 41 ml/min/1.73m^2 after age, sex and comorbidity were taken into account (**Study II**).
- In RENEXC, a randomized controlled clinical trial, 12 months of self-administered, individualized and regular strength- or balance exercise training, both combined with endurance exercise training, improved or maintained physical performance in both groups of patients representative of a non-dialysis dependent CKD population. There was an earlier onset of improvements in the strength group. Patients adhered to the program, confirming its feasibility (**Studies III and IV**).
- In RENEXC, 12 months of self-administered and regular strength- or balance exercise training, both combined with endurance exercise training, showed a slow decline in mGFR at an annual rate of 1.8ml/min/1.73m^2 in both groups. The strength group showed a significant decrease in albuminuria compared with the balance group, who maintained their level of albuminuria (**Study IV**).

Future Perspectives

RENEXC is the largest randomized controlled clinical trial to date, investigating the effects of regular exercise training with two different training modalities in patients with NDD-CKD. In addition to the research results presented in this thesis, there are numerous data that still need to be evaluated and analysed.

There are some possible cross-sectional baseline analyses in RENEXC that could be performed to investigate the following associations:

- Health related quality of life and self-perceived physical functioning in relation to measured physical performance and measured glomerular filtration rate
- The relationship between some markers of inflammation and measured glomerular filtration rate

Further effects after 12 months of exercise training will be analysed, comparing the strength group with the balance group, addressing the following subjects

- Heart rate variability, 24-hour blood pressure and left ventricular morphology and function
- Body composition measures and bone density
- Health related quality of life and self-perceived physical functioning
- Vascular calcification and serum lipids
- Markers of inflammation

It would also be of interest to perform studies based on RENEXC to increase knowledge about exercise training prescription in patients with NDD-CKD and how to provide an effective exercise training plan, which is easy to adhere to.

An important scientific challenge in the field of regular exercise training in patients with NDD-CKD would be a national or international multicentre randomized controlled clinical trial and this could be a future project.

All of these proposals are intended to further enhance scientific evidence so as to provide conditions for patients with CKD to receive physical exercise training as part of routine treatment in renal care units. The ultimate goal is to prevent impaired physical performance and concomitant complications.

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Popular summary of the thesis

The importance of physical performance, physical activity and exercise training for patients with chronic kidney disease is still underestimated. Low physical activity is considered to be one of the main causes of increased morbidity and mortality in the general population and this also applies to patients with chronic kidney disease. Patients with chronic kidney disease are characterized by an irreversible loss of kidney function. They usually require extensive medical treatment, which increases with the decline in kidney function. The kidneys are vital for the human body, when their function has declined to 10% or less of normal, dialysis treatment or kidney transplantation usually are required.

Chronic kidney disease

The kidneys' tasks include cleaning the blood and the body from waste products. They regulate body water, acid-base status and salt- and mineral balance. The kidneys regulate blood pressure, the production of hemoglobin and the activation of vitamins. Patients perceive a number of symptoms as kidney function declines. Among the most common symptoms are fatigue, nausea, loss of appetite, muscular weakness and fatigability, loss of strength and energy, inactivity and passivity, difficulty concentrating and depression. The symptoms become more pronounced with the decline in kidney function. Clinical status in combination with symptoms determines when dialysis treatment becomes necessary. Dialysis treatment can replace kidney function to a certain degree but does not replace the function of healthy kidneys. Some symptoms may persist despite dialysis and other medical treatment.

Physical performance and chronic kidney disease

Physical performance is often impaired in patients on maintenance dialysis treatment compared with healthy people. In general, patients achieved about 50 to 70% aerobic capacity compared with healthy people of the same sex and age, assessed with a cycle ergometer test. Muscular endurance and strength, balance capacity and fine motor skills are also impaired. In Sweden most renal care units offer their patients physiotherapy assessments and recommendations for exercise training.

Measurements of physical performance are a prerequisite to identify impairments before recommendations can be given. Regular exercise training among patients on maintenance dialysis improves their physical performance and symptoms often become fewer or more easily tolerable. In Sweden today, each patient on maintenance dialysis should, according to national guidelines, be offered an individualized plan for exercise training. In most other countries all over the world, even in the Western world, this is not the case. Scientific studies are still needed to increase the evidence concerning exercise training and physical performance in patients with chronic kidney disease.

*Physical performance and survival in patients who started dialysis treatment in Lund (**Study I**)*

For many years in Lund, most patients starting chronic dialysis treatment have been offered an assessment of physical performance. The measurements are comprehensive and evaluate endurance capacity, muscular strength in the legs and hands, muscular endurance in the lower limbs, balance capacity and fine motor skills in the hands. These measurements provided the base of my first scientific work, which investigated survival in relation to physical performance measures in patients who started on maintenance dialysis treatment between 1998 and 2006 in Lund. At the end of 2006, 22 patients were deceased and 112 were still alive. The different physical performance measures were compared at a group level. The deceased patients had a lower handgrip strength, muscular endurance in the lower legs and balance capacity compared with the patients who were still alive. Age, sex and comorbidity had a high impact on survival as well as on physical performance. However, it seemed that a higher level of physical performance in itself contributed to improved survival. Of special interest was that a decrease of 50% in handgrip strength in the left hand was associated with a three-fold increased risk of death.

Earlier exercise training studies in patients with chronic kidney disease

Earlier studies indicate that physical performance and physical activity decline with the decrease in kidney function. This has previously been reported for overall endurance capacity and strength in the arms and legs. Previous studies indicate that regular exercise training can counteract this trend. Unfortunately, the evidence is mostly based on small study groups, short intervention periods and patients not representative of the majority of patients with chronic kidney disease, i.e. the elderly and patients with a number of comorbidities. Taking this into account, RENEXC was designed and performed with the goal of comprising 150 representative patients with chronic kidney disease and not on maintenance dialysis treatment. The comprehensive measurements of physical performance and kidney function at baseline provided the base of my second scientific work (**Study II**).

Physical performance was impaired with reduced overall endurance, muscular endurance in the thighs and the lower legs, strength in the thighs and handgrip, and balance capacity in patients at baseline in RENEXC. A decrease in overall endurance, thigh strength, balance and fine motor skills was related to the decline in kidney function after age, sex and comorbidity had been taken into account (**Study II**).

RENEXC – RENal EXerCise – 12 months of exercise training in chronic kidney disease

RENEXC investigated how regular exercise training for 150 minutes per week during a period of 12 months affected physical performance (**Studies III and IV**) and kidney function (**Study IV**). All patients with chronic kidney disease treated at the outpatient clinic in Lund were invited to participate until 151 patients had been included, under the condition that exercise training did not present a risk to the patients. Each patient was randomized to either 90 minutes of strength- or balance exercise training, both combined with 60 minutes endurance exercise training. RENEXC was conducted between the autumn of 2011 and the summer of 2017.

The comprehensive assessments of physical performance in RENEXC included 10 different tests. Overall endurance was measured with the 6-minute walk test and a stair climbing test, muscular endurance in the thighs with the sit to stand test within 30 seconds and in the lower legs with heel rises and toe lifts, strength was measured in the thighs and with handgrip, balance capacity with leaning forward and a balance scale with 14 different items, and fine motor skills in the hands.

The exercise training prescription for each group was individualized and based on each patient's physical performance assessment. The patient could train at home or at a gym and contribute with individual preferences in consultation with the research physiotherapist. The prerequisite was that the program consisted of 90 minutes strength- or balance- and 60 minutes endurance training per week. The research physiotherapist phoned each patient once a week during the first three months and every second week for the rest of the period. Each patient documented training time and intensity in a training diary. These results showed a high acceptance and adherence to the program. After 4 months 83% of the participants reported on average about 150 minutes of exercise training per week and after twelve months about two thirds of the participants achieved that goal.

Effects of exercise training on physical performance in RENEXC

Physical performance was maintained or improved during the intervention period in both groups. Neither group showed a decline in any of the measures of physical performance during the study period. After 4 months, the strength group achieved an improvement in the walking- and stair climbing tests, muscular endurance in the thighs and lower legs, strength in the thighs and fine motor skills in the hands. The balance group also improved after 4 months, but in fewer tests namely in muscular endurance in the lower legs, strength in the thighs, balance and fine motor skills in the hands. After twelve months, both groups achieved improvements in the walking- and stair climbing tests, muscular endurance in the thighs and the lower legs, strength in the thighs, balance and fine motor skills in the hands. Handgrip strength and balance capacity, assessed with the scale of 14 different items, showed similar results after 12 months compared with baseline (**Studies III and IV**).

Effects of exercise training on kidney function in RENEXC

After 12 months, kidney function was measured and compared with baseline. A relatively slow decline in kidney function was measured and was the same in both groups. Albuminuria is considered to be a marker of progression of kidney dysfunction, cardiovascular morbidity and mortality, and was assessed during the study. The strength group showed a significant decline in albuminuria of about 33% after 12 months and the balance group had unchanged results (**Study IV**).

Summary

To summarize, the investigations in the present thesis increase knowledge about the relationships between physical performance, exercise training and chronic kidney disease. We found associations between better physical performance and survival in patients who started on chronic dialysis treatment. Impaired physical performance is already present patients in with chronic kidney disease not on maintenance dialysis. We found a relationship between impaired physical performance measures and the decline in kidney function, which was independent of age, sex and comorbidity. Physical performance was improved both by regular strength- or balance exercise training, both combined with endurance exercise training, during a period of 12 months. Both training modalities showed a slow decline in kidney function. In the strength group albuminuria decreased, in the balance group the levels were unchanged.

Future perspectives

RENEXC is to date the largest scientific study investigating the effects of regular exercise training on physical performance and kidney function in patients with chronic kidney disease not on maintenance dialysis. In addition to the results presented in this thesis, there are other RENEXC studies that have evaluated the relationships between kidney function and heart rate variability, kidney function and physical performance and body composition measures, and kidney function and vascular calcification. The effects of twelve months exercise training on for example heart rate variability, body composition measures and vascular calcification remain to be analysed.

A similar scientific study as RENEXC, conducted as a multi centre study with participation of different renal care units in Sweden or in Europe may be a future perspective to further enhance the evidence in the present field. The overriding aim is to improve the possibility for patients with chronic kidney disease to receive physical exercise training as part of routine treatment in renal care units in order to prevent impaired physical performance.

Populärvetenskaplig sammanfattning

Betydelsen av fysisk funktionsförmåga, fysisk träning och motion för patienter med kronisk njursjukdom är i dagens läge fortfarande underskattad. Låg fysisk aktivitet anses vara en av huvudorsakerna till ökad sjuklighet och dödlighet i den allmänna befolkningen, men även för patienter med kronisk njursjukdom (kronisk njursvikt). Dessa patienter har en bestående förlust av njurfunktion som kräver mera omfattande medicinsk behandling ju lägre njurfunktionen är. Det är livsnödvändigt att ha fungerande njurar och när njurfunktionen ligger kring 10% av det normala eller lägre behövs oftast behandling med dialys eller njurtransplantation.

Kronisk njursjukdom

Njurarnas uppgifter omfattar att rengöra blodet och kroppen från slaggprodukter. Njurarna reglerar kroppens vätskebalans, syra-bas-status och salt- och mineralbalans. Vidare styr de blodtrycksreglering, bildning av röda blodkroppar och aktivering av vissa vitaminer. Det finns många symtom som kan uppträda vid förlust av njurfunktion. Trötthet, illamående, mindre aptit, energilöshet, muskulär svaghet och lättare uttröttbarhet, fysisk inaktivitet och passivitet, nedsatt koncentrationsförmåga och depression kan förekomma. Symtomen är oftast mer uttalade ju lägre njurfunktionen är. Symtomen i kombination med den kliniska bilden avgör när dialysbehandling startas. Kronisk dialysbehandling kan till en viss del ersätta den egna njurfunktionen, men är inte likvärdig med friska njurar. Ofta kvarstå en del symtom trots dialys och annan medicinsk behandling.

Fysisk funktionsförmåga och kronisk njursjukdom

Fysisk funktionsförmåga är oftast nedsatt bland patienter i dialys jämfört med friska. Tidigare studier har visat att konditionen, mätt med en cykel belastningstest, låg på ca 50 till 70% jämfört med jämngamla friska av samma kön. Muskulär styrka och uthållighet, balansförmåga och finmotorik är också nedsatt hos patienter i dialysbehandling.

Mätning av fysisk funktionsförmåga är en förutsättning för att upptäcka påverkan så att patienten kan få anpassade råd om lämplig fysisk träning. Regelbunden fysisk träning bland patienter i dialys kan förbättra fysisk funktionsförmåga och även andra njursviktrelaterade symtom. På de flesta njurmedicinska enheter i Sverige finns det tillgång till fysioterapi. Varje patient i dialys i Sverige idag ska kunna erbjudas en individuell plan för fysisk träning. I de flesta andra länder i världen, även i västvärlden, kan detta inte erbjudas. Flera vetenskapliga studier krävs för att höja kunskapen om effekterna av fysisk träning hos patienter med kronisk njursjukdom.

*Fysisk funktionsförmåga och överlevnad hos patienter som startade i dialys i Lund (**Study I**)*

I Lund har man sedan många år erbjudit flertalet patienter som startar i kronisk dialysbehandling en bedömning av fysisk funktionsförmåga. Mätningarna är ganska omfattande och används för att bedöma kondition, muskelstyrka i händer och ben, uthållighet i underbensmuskler, balans och finmotorik i händerna. Dessa mätningar var förutsättningen för mitt första vetenskapliga arbete (**Studie I**). I den undersökte jag överlevnad i förhållande till fysisk funktionsförmåga hos patienter som startade i kronisk dialysbehandling mellan 1998 och 2006 i Lund. Vid slutet av 2006 hade 22 patienter avlidit och 112 var kvar i livet. De olika mätningarna av fysisk funktionsförmåga jämfördes på gruppnivå. De avlidna patienterna hade lägre handgreppstyrka, muskulär uthållighet i underbensmuskler och sämre balansförmåga. Ålder, kön och övrig sjuklighet hade stor betydelse för patienternas överlevnad och fysiska funktionsförmåga. Samtidigt fann vi att bättre fysisk funktionsförmåga i sig var associerad med en mindre risk att dö. Det var speciellt tydligt för handgreppstyrka i vänster hand, där en halvering av handgreppstyrkan var associerad med en tre gånger högre risk att dö.

Tidigare studier om fysisk träning vid kronisk njursjukdom

Tidigare studier rapporterar att fysisk aktivitet och fysisk funktionsförmåga avtar parallellt med förlusten av njurfunktionen. Förlusten av funktionsförmågan har huvudsakligen visats för kondition och muskelstyrka i armar och ben. Det finns en del studier som visar att regelbunden fysisk träning kan bryta trenden även tidigare i förloppet av kronisk njursjukdom. Denna kunskap baseras dock på korta interventionsperioder, små och icke representativa patientgrupper. Oftast deltog inte äldre och multisjuka patienter, som representerar flertalet patienter med kronisk njursjukdom. Därför planerade och genomförde vi i Lund en större studie, RENEXC, som var dimensionerad att omfatta tillräckligt många patienter och som siktade att inkludera representativa patienter med kronisk njursjukdom som inte var beroende av dialysbehandling eller var njurtransplanterade. Målet var att inkludera 150 patienter. En noggrann kartläggning av fysisk funktionsförmåga och njurfunktion av deltagarna i RENEXC vid start bildade basen till mitt andra delarbete (**Studie II**).

Vi fann nedsatt fysisk funktionsförmåga med lägre kondition, muskulär uthållighet både i lår- och underbensmuskler, styrka i lårmuskler och handgrepp och i balansförmåga hos patienterna vid start i RENEXC. Vi fann ett samband mellan nedsatt fysisk funktionsförmåga och graden av njurfunktionsnedsättning för kondition, lårmuskelstyrka, balans och finmotorik som var oberoende av ålder, kön och samsjuklighet. En 10% lägre njurfunktion var associerad med en 35 meter kortare gångsträcka och en 10% lägre lårmuskelstyrka. (**Studie II**)

RENEXC - RENal EXerCise – 12 månader fysisk träning vid kronisk njursjukdom

I RENEXC undersöktes fysisk funktionsförmåga noggrant med tio olika tester på ett standardiserat sätt. Kondition mättes med ett gångtest inom sex minuter och ett trapptest, muskulär uthållighet i lår- och underbensmuskler med ett test som mäter hur ofta man kan resa sig från sittande till stående samt tå- och hälhävningar, styrka i lårmusklerna och vid handgrepp, balansförmåga med att mäta räckvidden vid framåt böjande och med ett test bestående av 14 olika balansdeltester, och finmotorik i händerna med hjälp av ett plockprov.

I RENEXC undersökte vi hur regelbunden fysisk träning, bestående av 150 minuter per vecka under 12 månaders tid, påverkade fysisk funktionsförmåga (**Studier III + IV**) och njurfunktion (**Studie IV**). Alla patienter som följdes på njurmottagningen i Lund och ville delta fick erbjudande tills 151 patienter hade tackat ja. Varje patient lottades till antingen 90 minuters styrke- eller balansträning, båda i kombination med 60 minuters konditionsträning. RENEXC genomfördes mellan hösten 2011 och sommaren 2017.

Själva träningsprogrammet var upplagt så att varje patient fick ett program anpassat utifrån den enskilde patientens resultat i mätningarna av fysisk funktion. Patienten fick välja att träna hemma eller på ett gym och kunde själv bestämma detaljerna i samråd med forskningssjukgymnasten, så länge man höll sig till grundprogrammet utifrån lottad grupp: 90 minuter av antingen stryke- eller balansträning, båda i kombination med 60 minuters konditionsträning. Forskningssjukgymnasten ringde upp veckovis i början och varannan vecka efter tre månader. Därutöver var hon tillgänglig och nåbar utifrån den enskilde patientens behov. Varje patient dokumenterade sin träningstid och träningsintensitet i träningsdagboken. Utvärderingen av dessa data visar en stor acceptans och beredskap bland patienterna att följa ordinationen. Efter 4 månader var det 83% och efter 12 månader två tredjedelar av alla RENEXC patienter som rapporterade sin träning och uppfyllde i genomsnitt målet av 150 minuter träningstid per vecka.

Effekter av träning på fysisk funktionsförmåga i RENEXC

Fysisk funktionsförmåga förbättrades eller var bibehållen i båda grupperna. Styrkegruppen uppnådde efter 4 månaders träning förbättringar i gång- och trapptestet, i muskulär uthållighet i lårmuskler och underbensmuskler samt i lårmuskelstyrka och i finmotorik i händerna. Mätningar i balansgruppen visade förbättringar i muskulär uthållighet i underbensmuskler, lårmuskelstyrka, balans och finmotorik. Efter 12 månader uppvisade båda träningsgrupperna förbättringar i gång- och trapptestet, i muskulär uthållighet i lårmuskler och underbensmuskler, i lårmuskelstyrka, i balans med räckviddstestet och i finmotorik i båda händerna. Handgreppstyrka i båda händerna och mätning av balansförmåga med testet bestående av 14 enskilda mätningar var oförändrade efter 12 månader (**Studier III and IV**).

Effekter av träning på njurfunktion i RENEXC

Vid start och efter 12 månaders träning mättes njurfunktion. Patienterna i båda grupperna uppvisade en relativ långsam försämring. Albuminläckage i urinen är en markör för progresstakten av kronisk njursjukdomen och även för hjärt-kärl-sjuklighet och dödlighet. Styrkegruppen hade en markant minskning av albuminläckaget med ca 33% efter 12 månaders träning. Balansgruppen hade oförändrat albuminläckage efter 12 månaders träning (**Studie IV**).

Sammanfattning

Sammanfattningsvis har mina undersökningar ökat kunskapen om sambanden mellan fysisk funktionsförmåga, fysisk träning och kronisk njursjukdom. Vi fann ett samband mellan längre överlevnad och bättre fysisk funktionsförmåga hos patienter som startade i kronisk dialysbehandling. Påverkan på fysisk funktionspåverkan uppträdde relativt tidigt i förloppet av kronisk njursjukdom. Nedsatt fysisk funktionsförmåga var associerad med graden av njurfunktionsförlust oberoende av ålder, kön och samsjuklighet. Fysisk funktionsförmåga förbättrades genom regelbunden fysisk träning under 12 månaders tid, oberoende av vilken träningsmodalitet patienterna lottades till: styrke- eller balans- i kombination med konditionsträning. Vidare verkar det som att båda träningsmodaliteter hade positiva effekter på njurfunktionen med en relativ långsam förlust av njurfunktionen under den 12 månader långa interventionsperioden. Styrkegruppen uppvisade ett minskat albuminläckage, medan balansgruppens albuminläckage var oförändrat.

Framtiden

RENEXC är hittills den största vetenskapliga studien som undersöker effekter av regelbunden fysisk träning på patienter med kronisk njursjukdom som inte är beroende av dialys. Förutom undersökningsresultat som jag har presenterat i min avhandling, finns det andra data som också har utvärderats såsom samband mellan njurfunktion och hjärtrytmvariabilitet, mellan njurfunktion, fysisk funktionsförmåga och kroppssammansättning, samt mellan njurfunktion och kärlförkalkning. Träningseffekter på hjärtrytmvariablitet, hjärtfunktion, kroppssammansättning, livskvalitet och självskattad fysisk funktionsförmåga, liksom kärlförkalkning och inflammation återstår att undersöka.

En liknande vetenskaplig studie som RENEXC med deltagande av flera olika njurmedicinska enheter i Sverige eller i Europa skulle kunna utgöra ett framtidsprojekt för att höja den vetenskapliga evidensen ytterligare. Målet är att skapa förutsättningar för patienter med kronisk njursjukdom att erbjudas fysisk träning som del av den njurmedicinska behandlingen inte minst ur ett preventionsperspektiv.

Populärwissenschaftliche Zusammenfassung

Die Bedeutung der körperlichen Leistungsfähigkeit, des körperlichen Trainings und der körperlichen Aktivität für Patienten mit chronischer Nierenerkrankung ist auch heutzutage weiterhin als unterbewertet einzuschätzen. Geringe physische Aktivität wird als eine der Hauptursachen für die hohe Erkrankungsraten und Sterblichkeit in der Bevölkerung angesehen, und gilt auch für Patienten mit chronischer Nierenerkrankung. Eine chronische Nierenerkrankung geht mit dem fortschreitenden Verlust der Nierenfunktion einher, wird auch als Niereninsuffizienz bezeichnet und bedarf intensiver nierenfachärztlicher Betreuung und Behandlung. Die Funktion der Niere ist lebensnotwendig, bei Abnahme der Nierenfunktion auf etwa 10% oder niedriger wird die unterstützende Behandlung mit der Dialyse eingeleitet, wenn nicht alternativ eine Nierentransplantation durchgeführt werden kann.

Chronische Nierenerkrankung

Die Aufgaben der Nieren sind sehr vielfältig und beinhalten die Reinigung des Blutes und des Körpers von Stoffwechselendprodukten. Die Nieren sorgen für eine ausgewogene Balance des Wassergehaltes im Körper, des Säure-Basen Haushalts und der Körpersalze und -mineralien. Sie sind an der Regulierung der Blutbildung, des Blutdrucks und einiger Vitaminspiegel beteiligt. Symptome, die durch den Verlust der Nierenfunktion auftreten, können sehr vielgestaltig sein. Müdigkeit, Übelkeit, geringer Appetit, Energielosigkeit, Muskelschwäche und leichte Ermüdbarkeit, körperliche Inaktivität und Passivität, Konzentrationsstörungen und Depression können vorkommen. Die Symptome sind meist umso ausgeprägter, je niedriger die Nierenfunktion ist. Die Symptome zusammen mit dem klinischen Bild sind auschlaggebend dafür, wann die Behandlung mit der Dialyse ergänzend eingeleitet wird. Die chronische Dialysebehandlung kann die Nierenfunktion zum Teil ersetzen, ist jedoch mit gesunden Nieren nicht vergleichbar. Ein Teil der Symptome kann trotz chronischer Dialysebehandlung und anderer begleitender Behandlungen fortbestehen.

Körperliche Leistungsfähigkeit und chronische Nierenerkrankung

Die körperliche Leistungsfähigkeit ist bei Patienten mit chronischer Dialysebehandlung im Vergleich mit Gesunden meist reduziert. Frühere Studien konnten zeigen, dass beispielsweise die Kondition, gemessen mit dem Fahrradergometer, Werte von etwa 50 bis 70% im Vergleich mit gleichaltrigen Gesunden erreichte. Sowohl Muskelkraft, Muskelausdauer, Gleichgewicht sowie Feinmotorik können bei Patienten mit chronischer Dialyse betroffen sein.

Die Messung der körperlichen Leistungsfähigkeit ist Voraussetzung, um etwaige Beeinträchtigungen zu erkennen und gegebenenfalls entsprechende Empfehlungen zu geeignetem körperlichen Training aussprechen zu können. Körperliches Training bei Patienten mit chronischer Dialyse hat Wirkung gezeigt, sowohl bei der Verbesserung der eingeschränkten körperlichen Leistungsfähigkeit als auch bei der Linderung, der mit der Nierenerkrankung einhergehenden Symptome. In den meisten Nierenzentren in Schweden wird Patienten mit chronischer Dialysebehandlung Physiotherapie angeboten. In den meisten anderen Ländern der Welt, ist dies auch heutzutage nicht Teil des Leistungsspektrums. Weitere wissenschaftliche Studien werden gebraucht, um den Kenntnisstand über die Effekte körperlichen Trainings bei Patienten mit chronischer Nierenerkrankung zu erhöhen.

Körperliche Leistungsfähigkeit und Überleben von Dialysepatienten in Lund

An der Nierenklinik in Lund hat man seit vielen Jahren einer Vielzahl von Patienten, die mit chronischer Dialysebehandlung begonnen haben, gleichzeitig die Beurteilung der körperlichen Leistungsfähigkeit angeboten. Die Messungen waren umfangreich und dienten der Bewertung von Kondition, Muskelkraft in den Beinen und Armen, muskulärer Ausdauer in den Unterschenkeln, sowie von Gleichgewicht und Feinmotorik in den Händen. Diese Ergebnisse bildeten die Grundlage meiner ersten wissenschaftlichen Arbeit (**Studie I**). Hier untersuchte ich den Zusammenhang zwischen körperlicher Leistungsfähigkeit und Überleben bei den Patienten, die in Lund zwischen 1998 und 2006 mit der chronischen Dialysebehandlung begonnen hatten. Ende 2006 waren 22 Patienten verstorben und 112 lebten. Die verschiedenen Messergebnisse wurden auf Gruppenniveau miteinander verglichen. Die Gruppe der verstorbenen Patienten zeigte deutlich geringere Resultate bei der Greifkraft, der muskulären Ausdauer in den Unterschenkeln und auch beim Gleichgewicht. Das Alter, das Geschlecht und die Begleiterkrankungen hatten großen Einfluss auf das Überleben und die körperliche Leistungsfähigkeit. Gleichzeitig fanden wir auch, dass eine bessere körperliche Leistungsfähigkeit an sich mit einem geringeren Risiko zu streben einherging. Dies wurde besonders deutlich bei den Messungen der Greifkraft in der linken Hand, bei der eine Halbierung mit einem dreifachen erhöhten Sterblichkeitsrisiko verbunden war.

Frühere Studien zu körperlichem Training bei chronischer Nierenerkrankung

Ergebnisse früherer Studien zeigen, dass die körperliche Aktivität und Leistungsfähigkeit parallel mit dem Verlust der Nierenfunktion abnahmen. Die Abnahme der Leistungsfähigkeit zeigte sich vor allem im Hinblick auf Kondition und Muskelkraft in den Armen und Beinen. Einige Studien weisen darauf hin, dass diesem Trend auch frühzeitig im Verlauf der chronischen Nierenerkrankung entgegengewirkt werden kann. Diese Erkenntnisse basieren doch auf kurzen Interventionsperioden sowie kleinen und nicht repräsentativen Patientengruppen. Meist wurden vor allem die Älteren und die Patienten mit mehreren Begleiterkrankungen, die einen Großteil der Patienten mit chronischer Nierenerkrankung ausmachen, ausgeschlossen. Deshalb planten und verwirklichten wir in Lund eine größere Studie, RENEXC, die mit einer ausreichenden Anzahl von Patienten mit chronischer Nierenerkrankung, die noch keiner Dialyse oder Nierentransplantation bedurften, dimensioniert war. Das Ziel waren 150 teilnehmende Patienten. Eine gründliche Beurteilung der körperlichen Leistungsfähigkeit und der Nierenfunktion eines jeden Patienten standen am Anfang. Diese Daten bildeten die Grundlage meiner zweiten wissenschaftlichen Arbeit. (**Studie II**)

Die beeinträchtigte körperliche Leistungsfähigkeit bei den RENEXC Patienten zeigte sich bei den Messungen der Kondition, der muskulären Ausdauer in den Ober- und Unterschenkeln, der Muskelkraft in den Oberschenkeln und Unterarmen sowie im Gleichgewicht. Die Messwerte für Kondition, Oberschenkelkraft, Gleichgewicht und Feinmotorik in der Hand korrelierten mit dem Grad der abnehmenden und gemessenen Nierenfunktion. Eine 10-prozentige Abnahme der Nierenfunktion war mit einer 35 Meter kürzeren Gehstrecke und einer 10% geringeren Muskelkraft im Oberschenkel verbunden. (**Studie II**)

RENEXC – RENal EXerCise – 12 Monate körperliches Training bei chronische Nierenerkrankung

In RENEXC wurde die körperliche Leistungsfähigkeit mit 10 unterschiedlichen Tests standardisiert gemessen. Kondition wurde mit einem 6-Minuten-Geh-Test und einem Treppensteig-Test gemessen. Die muskuläre Ausdauer in den Oberschenkeln wurde mit der Anzahl der Wechsel von der sitzenden zur stehenden Position innerhalb von 30 Sekunden erfasst, und in den Unterschenkeln mit den wiederholten Hebungen in den einseitigen Zehen- und Fersenstand. Weiterhin erfolgten die Messung der Kraft in den Oberschenkeln und der Greifkraft, des Gleichgewichts mit der Messung der Reichweite beim Vornüberbeugen und mit einem weiteren Test, der aus 14 Teiltesten besteht, sowie die Messung der Feinmotorik in den Händen mit einem Fingeraufnahme-Test.

In RENEXC untersuchten wir, wie regelmäßiges körperliches Training, bestehend aus 150 Minuten pro Woche über insgesamt 12 Monate, die physische

Leistungsfähigkeit (**Studien III und IV**) und die Nierenfunktion (**Studie IV**) beeinflusst. Alle Patienten, die in der nephrologischen Ambulanz in Lund betreut wurden und an RENEXC teilnehmen wollten, wurden aufgenommen, bis die Anzahl von 151 erreicht war. Jeder Patient wurde entweder zu 90 Minuten Kraft- oder Gleichgewichtstraining, beides in Kombination mit 60 Minuten Konditionstraining, zugelost. RENEXC wurde zwischen Herbst 2011 und Frühsommer 2017 durchgeführt.

Das Trainingsprogramm war so konzipiert, dass jeder Patient ein individuelles Programm, basierend auf seinen Ergebnissen der körperlichen Leistungsfähigkeit, erhielt. Jeder Patient konnte selbst entscheiden, ob er zu Hause oder im Fitness-Studio trainieren wollte und konnte auch auf Details des Programmes in Zusammenarbeit mit dem Forschungsphysiotherapeuten Einfluss nehmen, so lange dem Grundprinzip von entweder 90 Minuten Kraft- oder Gleichgewichtstraining in Kombination mit 60 Minuten Konditionstraining Rechnung getragen wurde. Der Forschungsphysiotherapeut rief jeden Patienten zu Beginn wöchentlich und nach drei Monaten alle zwei Wochen an, und war darüber hinaus entsprechend des Bedarfs für den Patienten leicht erreichbar. Jeder Patient war gebeten, ein Trainingstagebuch zu führen, um seine trainierte Zeit und Intensität zu dokumentieren. Die Auswertung dieser Daten zeigte eine große Akzeptanz und Bereitschaft, das Training durchzuführen. Nach 4 Monaten waren es 83% und nach 12 Monaten zwei Drittel aller teilnehmenden Patienten, die ihr Training dokumentierten und im Durchschnitt das Ziel von 150 Minuten Training pro Woche erreichten.

Effekte körperlichen Trainings auf die körperliche Leistungsfähigkeit in RENEXC

In beiden Trainingsgruppen verbesserte sich die körperliche Leistungsfähigkeit oder konnte stabilisiert werden. Die Krafttrainingsgruppe erreichte nach 4 Monaten Training Verbesserungen im 6-Minuten-Geh-Test und Treppensteig-Test, in der muskulären Ausdauer in den Ober- und Unterschenkeln, in der Kraft im Oberschenkel als auch in der Feinmotorik in den Händen. Die Gleichgewichtstrainingsgruppe verbesserte ihre muskuläre Ausdauer in den Unterschenkeln, die Kraft in den Oberschenkeln, das Gleichgewicht und die Feinmotorik. Nach 12 Monaten zeigten beide Gruppen Verbesserungen im 6-Minuten-Geh-Test und Treppensteig-Test, in der muskulären Ausdauer in den Ober- und Unterschenkeln, in der Kraft in den Oberschenkeln, im Gleichgewicht und in der Feinmotorik in den Händen. Die Greifkraft und die Messung des Gleichgewichts mit dem Test bestehend aus 14 Teiltesten zeigten unveränderte Ergebnisse nach 12 Monaten. (**Studien III und IV**)

Effekte körperlichen Trainings auf die Nierenfunktion in RENEXC

Zu Beginn und nach 12 Monaten wurde die Nierenfunktion gemessen. Beide Trainingsgruppen zeigten während dieser Zeit einen relativ langsamen Verlust der Nierenfunktion. Der Albumingehalt im Urin ist ein Marker für den Verlust der Nierenfunktion sowie ein Risikomarker für Herz-Kreislauf-Ereignisse wie Herzinfarkt oder Schlaganfall und für die Sterblichkeit. Die Krafttrainingsgruppe zeigte nach 12 Monaten eine mit 33% signifikante Abnahme des Albumingehaltes im Urin. Die Gleichgewichtstrainingsgruppe zeigte nach 12 Monaten unveränderte Werte. (**Studie IV**)

Zusammenfassung

Meine Untersuchungen haben den Kenntnisstand über den Zusammenhang zwischen körperlicher Leistungsfähigkeit, körperlichen Trainings und chronische Nierenerkrankung erhöht. Wir fanden einen Zusammenhang zwischen höherer Sterblichkeit und eingeschränkter körperlicher Leistungsfähigkeit bei Patienten mit chronischer Nierenerkrankung, die mit chronischer Dialysebehandlung begonnen hatten. Die Beeinträchtigung der körperlichen Leistungsfähigkeit tritt relativ früh im Verlauf der chronischen Nierenerkrankung auf. Der Grad der Beeinflussung der körperlichen Leistungsfähigkeit korrelierte mit dem Grad des Verlustes der Nierenfunktion unabhängig vom Alter, vom Geschlecht und den Begleiterkrankungen. Die körperliche Leistungsfähigkeit konnte durch regelmäßiges körperliches Training, unabhängig vom zugelosten Programm (Kraft- oder Gleichgewichts- in Kombination mit Konditionstraining) innerhalb 12 Monaten bei den Patienten mit chronischer Nierenerkrankung verbessert werden. Des Weiteren scheinen beide Trainingsprogramme positive Effekte auf die Nierenfunktion mit einem relativ langsamen Verlust der Nierenfunktion während der 12 Monaten körperlichen Trainings zu haben. Die Krafttrainingsgruppe zeigte eine Abnahme des Albumingehaltes im Urin, der in der Gleichgewichtsgruppe unverändert war.

Zukunftspläne

RENEXC ist bis heute die größte wissenschaftliche Studie, die Effekte regelmäßigen körperlichen Trainings auf Patienten mit chronischer Nierenerkrankung, die nicht dialysepflichtig sind, untersucht. Außer den Ergebnissen, die in dieser Arbeit präsentiert werden, gibt es andere Daten, die bereits ausgewertet wurden, wie zum Beispiel der Zusammenhang zwischen Nierenfunktion und Herzfrequenzvariabilität, zwischen Nierenfunktion, körperlicher Leistungsfähigkeit und der Muskelmasse, als auch zwischen Nierenfunktion und Gefäßverkalkung. Effekte körperlichen Trainings auf die Herzfrequenzvariabilität, Herzfunktion, die Muskelmasse, Lebensqualität und

Selbsteinschätzung der körperlichen Leistungsfähigkeit, sowie auf die Gefäßverkalkung und systemische Entzündungsprozesse stehen noch aus.

Eine wissenschaftliche Studie in Anlehnung an RENEXC mit der Teilnahme mehrerer nationaler oder internationaler Nierenzentren könnte ein Zukunftsprojekt sein, welches die wissenschaftliche Evidenz weiter steigern könnte. Das Ziel ist Voraussetzungen zu schaffen, jedem Patienten mit chronischer Nierenerkrankung, körperliches Training im Rahmen der nephrologischen Behandlung anzubieten.

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Appendix

A	*Testbattery in Lund*
B	*Berg balance Scale (1-3/3)*
C	*Borg Scale*
D	*Training diary*

Appendix A Testbattery in Lund

Testprotokoll

Datum:... Sjukgymnast:……………………………

Namn:…………………………………………………….. Pers.nr:…………………..

Ålder:…………….. Kön:……………… Längd:……………Vikt:………………

Handgreppstyrka	Hö	Vä
”Jag vill att du håller handtaget såhär och trycker så hårt du kan.”	1………	1……….
”Är du färdig? Tryck så hård du kan.”	2……....	2……….
”Hårdare!....hårdare!......slappna av.”	3……….	3………..
	m……..	m……….

Plockprov	Hö	Vä
seende ________________________________	………	…………
blundande ______________________________	……….	…………..

Balanstest (Funktional reach)		Hö / Vä-hänt		
”Stå som vanligt”	1	I….....	II….....	dif…..
”Sträck dig så långt fram du kan utan att tappa Balansen, med knytnäven i höjd med måttstocken.”	2	I……..	II…….	dif...... m…..
	3	I……..	II…….	dif......

Tåhävningar	Hö	Vä	Både
”Lyft upp foten från golvet och håll den där, medan du gör så många tåhävningar du kan på det andra benet.”	………	……...	……….

Hälhävningar	Hö	Vä	Både
”Lyft upp foten ifrån golvet och håll den där, medan du gör så många hälhävningar, dvs framfotslyft som d kan på det andra benet.”	……….	………	………..

Isometrisk Quadricepsstyrka

”Försök nu sträcka benet allt vad du orkar.”

Hö u-benslängd:……………cm 1……. 2…… 3…….. m……. =……..Kgxcm

Vä u-benslängd:……………cm 1……. 2…… 3…….. m……. =……..Kgxcm

Trapptest

”Gå i ditt normala tempo upp och ner för den här trappan,
utan att stanna och göra paus, så många gånger som du orkar.” …….………………………...

Appendix B Berg balance scale (1/3)

Berg Balance Scale

Name: ___________________________________ Date: ____________________

Location: _________________________________ Rater: ____________________

ITEM DESCRIPTION	SCORE (0-4)
Sitting to standing	________
Standing unsupported	________
Sitting unsupported	________
Standing to sitting	________
Transfers	________
Standing with eyes closed	________
Standing with feet together	________
Reaching forward with outstretched arm	________
Retrieving object from floor	________
Turning to look behind	________
Turning 360 degrees	________
Placing alternate foot on stool	________
Standing with one foot in front	________
Standing on one foot	________

Total ________

GENERAL INSTRUCTIONS
Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:

- the time or distance requirements are not met
- the subject's performance warrants supervision
- the subject touches an external support or receives assistance from the examiner

Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing is a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5, and 10 inches. Chairs used during testing should be a reasonable height. Either a step or a stool of average step height may be used for item # 12.

Appendix B (2/3)

Berg Balance Scale

SITTING TO STANDING
INSTRUCTIONS: Please stand up. Try not to use your hand for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or stabilize
( ) 0 needs moderate or maximal assist to stand

STANDING UNSUPPORTED
INSTRUCTIONS: Please stand for two minutes without holding on.
( ) 4 able to stand safely for 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 seconds unsupported
( ) 1 needs several tries to stand 30 seconds unsupported
( ) 0 unable to stand 30 seconds unsupported

If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL
INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely for 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to able to sit 30 seconds
( ) 1 able to sit 10 seconds
( ) 0 unable to sit without support 10 seconds

STANDING TO SITTING
INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assist to sit

TRANSFERS
INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cuing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

STANDING UNSUPPORTED WITH EYES CLOSED
INSTRUCTIONS: Please close your eyes and stand still for 10 seconds.
( ) 4 able to stand 10 seconds safely
( ) 3 able to stand 10 seconds with supervision
( ) 2 able to stand 3 seconds
( ) 1 unable to keep eyes closed 3 seconds but stays safely
( ) 0 needs help to keep from falling

STANDING UNSUPPORTED WITH FEET TOGETHER
INSTRUCTIONS: Place your feet together and stand without holding on.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 seconds
( ) 1 needs help to attain position but able to stand 15 seconds feet together
( ) 0 needs help to attain position and unable to hold for 15 seconds

Appendix B (3/3)

Berg Balance Scale continued…

REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING
INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)

( ) 4 can reach forward confidently 25 cm (10 inches)
( ) 3 can reach forward 12 cm (5 inches)
( ) 2 can reach forward 5 cm (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION
INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.

( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING
INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)

( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

TURN 360 DEGREES
INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.

( ) 4 able to turn 360 degrees safely in 4 seconds or less
( ) 3 able to turn 360 degrees safely one side only 4 seconds or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cuing
( ) 0 needs assistance while turning

PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED
INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.

( ) 4 able to stand independently and safely and complete 8 steps in 20 seconds
( ) 3 able to stand independently and complete 8 steps in > 20 seconds
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete > 2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

STANDING UNSUPPORTED ONE FOOT IN FRONT
INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)

( ) 4 able to place foot tandem independently and hold 30 seconds
( ) 3 able to place foot ahead independently and hold 30 seconds
( ) 2 able to take small step independently and hold 30 seconds
( ) 1 needs help to step but can hold 15 seconds
( ) 0 loses balance while stepping or standing

STANDING ON ONE LEG
INSTRUCTIONS: Stand on one leg as long as you can without holding on.

( ) 4 able to lift leg independently and hold > 10 seconds
( ) 3 able to lift leg independently and hold 5-10 seconds
( ) 2 able to lift leg independently and hold ≥ 3 seconds
( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.
( ) 0 unable to try of needs assist to prevent fall

( ) TOTAL SCORE (Maximum = 56)

Appendix C Borg scale

20 Point Borg Scale		
RPE Rate of Perceived Exertion		
POINT	EFFORT	DESCRIPTION
6	No Exertion	Little to no movement, very relaxed
7	Extremely Light	Able to maintain pace
8		
9	Very Light	Comfortable and breathing harder
10		
11	Light	Minimal sweating, can talk easily
12		
13	Somewhat Hard	Slight breathlessness, can talk
14		Increased sweating, still able to hold conversation but with difficulty
15	Hard	Sweating, able to push and still maintain proper form
16		
17	Very Hard	Can keep a fast pace for a short time period
18		
19	Extremely Hard	Difficulty breathing, near muscle exhaustion
20	Maximally Hard	STOP exercising, total exhaustion

Appendix D Training diary

T R Ä N I N G S D A G B O K **Patientnamn:**________________ **Personnummer:**_________-_____

År	dag	Trän tid/dag		dag	Trän tid/dag		dag	Trän tid/dag		dag	Trän tid/dag		dag	Trän tid/dag	
Kondition/ Uppvärmning	Trän tid	Borg		Trän tid	Borg		Trän tid	Borg		Trän tid	Borg		Trän tid	Borg	
Kommentar															
Övning1	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg
Kommentar															
Övning 2	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg
Kommentar															
Övning3	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg
Kommentar															
Övning 4	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg	Rep	ggr	Borg
Kommentar															

ID-NR:________ Kort-NR:_______