Exercise using the Borg scale in chronic kidney disease - A self-administered individualised long-term exercise programme

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Exercise using the Borg scale in patients with chronic kidney disease

A self-administered individualised long-term exercise programme

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Exercise using the Borg scale in patients with chronic kidney disease

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Philippa Svensson

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) in Medical Science at the Faculty of Medicine at Lund University to be publicly defended on 23rd of April at 09.00 in Alwall House Lecture Hall, Department of Nephrology, Barngatan 2, Lund, Sweden.

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Abstract:

The aims of this thesis were to investigate the effects of 12 months self-administered, individualised exercise on physical performance and health-related quality of life (HRQOL), and using the Borg scale for safe and efficacious exercise prescription and monitoring in patients with CKD 3-5.

Methods
151 patients were randomised to balance (BG) or resistance (RG) exercise, both combined with aerobic endurance exercise. Exercise intensity was prescribed with the Borg Rating of Percieved Exertion (RPE) scale. Aerobic endurance exercise was prescribed with RPE 13-15, 60 minutes/week. Balance and resistance exercise were prescribed with RPE 13-17, 90 minutes/week. Physical performance and HRQOL were evaluated at 0, 4, 8 and 12 months.

Results
Physical performance was significantly improved or maintained: (***= p<0.001, **= p<0.01, *= p<0.05) 6MWT (BG***, RG***), stair climbing (BG ***, RG***): Functional Reach (BG**, RG**) , isometric quadriceps strength right,left (BG**, **, RG***, **), 30 second sit-to-stand (BG**, RG***), toe lifts (BG***, RG**), heel rises (BG***, RG***) and Moberg pick up test eyes open right (RG***) left (BG*, RG**), eyes closed right (BG*, RG***), left (RG*), with no difference between groups. Most aspects of HRQOL were maintained in both groups. RG showed significantly more favorable trajectories for HRQOL over time compared with BG. Patients performed exercise safely within the prescribed RPE, with high adherence over 12 months. There was a wide range of weekly duration, with a signficant association betweeen baseline results for 6MWT and weekly duration*. Patients signficantly improved all aspects of physical performance, irrespective of performed weekly duration, indicating that even short durations can improve physcial performance when RPE was maintained within the exercise prescription.

Conclusion
The Borg scale was safe and efficacious for prescribing and monitoring self-administered and individualised exercise, significantly improving or maintaining physical performance and most aspects of HRQOL after 12 months in patients with CKD.

Key words: Chronic Kidney Disease, Exercise training, The Borg scale, Physical Performance, Aerobic endurance, Balance, Resistance, Health-related Quality of Life

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MADE IN SWEDEN

To all individuals living with chronic kidney disease

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List of papers

This thesis is based on the following publications or manuscripts:

Paper 1

Randomized Controlled Trial of Exercise in CKD -The RENEXC Study.

Matthias Hellberg, Peter Höglund, Philippa Svensson, Naomi Clyne.

Kidney International Reports. 2019 Apr 9;4(7):963-976.

Paper 2

Health-related quality of life after 12 months self-administered exercise in patients with CKD 3-5 – a sub study of RENEXC, a randomized controlled trial.

Philippa Svensson, Matthias Hellberg, Anita Wisén, Naomi Clyne.

In manuscript.

Paper 3

The Borg scale is a sustainable method for prescribing and monitoring self-administered aerobic endurance exercise in patients with chronic kidney disease.

Philippa Svensson, Matthias Hellberg, Yunan Zhou, Anita Wisén, Naomi Clyne.

European Journal of Physiotherapy. 2022;25(5):265-273.

Paper 4

The Borg scale is safe and efficacious for prescribing and monitoring self-administered balance and resistance exercise in patients with chronic kidney disease – a post-hoc analysis of RENEXC, a randomized controlled trial.

Philippa Svensson, Matthias Hellberg, Anita Wisén, Naomi Clyne.

Journal of Rehabilitation Medicine. 2025;57: jrm44158

Abbreviations

ACSM	American College of Sports Medicine
ATP	adenosine triphosphate
BG	balance group
BBS	Berg balance scale
BMI	body mass index
CKD	chronic kidney disease
DEXA	dual-energy X-ray absorptiometry
DiaTT	Dialysis training therapy
EXCITE	EXerCise Introduction To Enhance Performance in Dialysis
EQUAL	European QUALity study
FITT-VP	frequency, intensity, time, type – volume, progression
FR	functional reach
GFR	glomerular filtration rate
eGFR	estimated glomerular filtration rate
mGFR	measured glomerular filtration rate
HD	haemodialysis
HGS	hand grip strength
HRQOL	health-related quality of life
IQS	isometric quadriceps strength
ISWT	incremental shuttle walk test
KDIGO	Kidney Disease Improving Global Outcomes
KDQOL-SF	Kidney Disease Quality of Life – Short Form
KRT	kidney replacement therapy
KT	kidney transplant
LANDMARK	Longitudinal Assessment of Numerous Discrete Modifications of Atherosclerotic Risk Factors in Kidney Disease
MCS	mental component summary
MET	metabolic equivalent

MCID	minimal clinically important difference
MDC	minimal detectable change
PCr	phosphocreatine
PCS	physical component summary
PD	peritoneal dialysis
PROMs	patient reported outcome measures
RCT	randomised controlled trial
RENEXC	RENal EXerCise
RG	resistance group
RM	repetition maximum
ROS	reactive oxygen species
RPE	rating of perceived exertion
SEM	standard error of measurement
SMART	specific, measurable, achievable, realistic, timed
SPPB	short physical performance battery
STS	sit-to-stand
STS30	30 second sit-to-stand
SF-36	The Medical Outcomes Study Short Form 36
TUG	timed up and go
U-ACR	urine-albumin-creatinine ratio
UPS	ubiquitin-proteasome system
VO_2max	the maximal oxygen consumption achieved during a maximal exercise test
VO_2peak	the highest oxygen uptake reached during an exercise test
WHO	World health organization
6MWT	6-minute walk test
Δ	delta

Thesis at a glance

Aim	Design	Conclusion
Paper 1 To compare the effects of 12 months balance versus resistance exercise on physical performance.	A single-centre RCT (RENEXC). 151 patients randomised to 12 months of self-administered, individualised balance or resistance exercise, combined with aerobic endurance exercise. Physical performance was evaluated at 0,4,8 and 12 months. Intention to treat analysis.	Significant improvements in all aspects of physical performance,with no difference between groups.
Paper 2 To compare the effects of 12 months balance versus resistance exercise on HRQOL.	A single centre RCT - a prespecified substudy of RENEXC. Intention to treat analysis.	Resistance + aerobic exercise demonstrated significantly more favorable trajectories for HRQOL compared with balance + aerobic exercise. Both groups maintained or improved most subscales in KDQOL-SF, indicating positive effects of both exercise modalities on HRQL in patients with CKD 3-5.
Paper 3 To examine safety, adherence, and performance of self-administered aerobic endurance exercise prescribed and monitored with the Borg RPE scale, and the relationships between performed exercise intensity and exercise duration and change in walking distance.	A post hoc analysis of the RENEXC trial with all patients pooled into one cohort. Per protocol analysis.	The Borg RPE scale was a safe and efficacious method for prescribing and monitoring self-administered aerobic endurance exercise in patients with CKD, with good adherence during the 12 month intervention period. A RPE between 13–15 improved walking distance both in well-functioning and deconditioned patients, within a wide range of weekly exercise duration.
Paper 4 To examine adherence, performance, and safety of self-administered balance and resistance exercise prescribed and monitored with the Borg RPE scale, and the relationships between performed exercise intensity and exercise duration and change in balance or strength.	A post hoc analysis of the single centre RCT (RENEXC). Per protocol analysis.	The Borg RPE scale was a safe and efficacious method for prescribing and monitoring self-administered balance or resistance exercise in patients with CKD, with good adherence during the 12 month intervention period. A RPE between 13-17 improved balance and strength both in well-functioning and deconditioned patients, within a wide range of weekly exercise duration.

Introduction

Chronic kidney disease (CKD) is a growing global health issue and estimated to become the fifth leading cause of death by 2040. When kidney function declines, patients experience symptoms such as fatigue, loss of strength, and physical inactivity. This results in a decline in physical performance that can affect activities in daily life. Patients with CKD experience lower health-related quality of life compared to healthy individuals.

As knowledge of the benefits of physical activity and exercise in patients with CKD increases, it is important to find a sustainable way to integrate exercise in the standard care of these patients. Most studies comprising patients with CKD have focused on patients on maintenance dialysis, on in-centre exercise programmes or exercise programmes with intervention periods less than three months, often comprising patients with little or no comorbidities. There is a need for more knowledge about self-administered exercise in the earlier stages of CKD, as well as of the effects of exercise during longer intervention periods with inclusion criteria that reflect clinical reality. The RENal EXerCise (RENEXC) trial was created to address this knowledge gap, focusing on a sustainable way for integrating exercise into the everyday life of patients with CKD. All studies in this thesis are based on data from the RENEXC-trial.

It is essential that self-administered exercise can be performed in a safe yet efficacious way. However, little is known about the best method of prescribing and monitoring self-administered exercise intensity in patients with CKD. In the RENEXC-trial we used the Borg Rating of Perceived Exertion scale for the prescription and monitoring of exercise intensity for aerobic endurance, balance, and resistance exercise. Although the Borg scale has been used to prescribe aerobic exercise, and in some studies resistance exercise, to our knowledge, no studies have examined the use of the Borg scale for prescribing balance exercise in patients with CKD or examined its use for different types of exercise.

This thesis aims to investigate the effects of self-administered, individualised, long-term exercise on physical performance and health-related quality of life, and how exercise could safely and efficaciously be prescribed and monitored in patients with CKD 3-5 using the Borg scale.

Background

The kidneys

The kidneys are vital organs, responsible for maintaining homeostasis in the body by removing waste products, regulating fluid balance and maintaining electrolyte and acid-base equilibrium. The kidneys also have endocrine functions such as production of renin, activation of vitamin D, and production of erythropoietin and endothelin.

The kidney's functional units consist of the outer cortex and the inner renal medulla. The nephron is the basic structural and functional unit of the kidney, consisting of glomerular capillaries that are enclosed by Bowman's capsule, which is the first part of the tubular system. A kidney consists of about one million nephrons. The first step of urine formation begins with the glomerular filtration of plasma, where the net filtration pressure forces fluids and solutes of small molecular size through pores in the capillary walls of the glomerulus into the lumen of Bowman's capsule. The substances that are filtered in the glomeruli are water, electrolytes such as sodium, potassium, calcium, magnesium, bicarbonate, phosphate and chloride, and non-electrolytes such as amino-acids, small proteins, glucose, urea, uric acid and creatinine. The second step in urine formation is tubular reabsorption and secretion, where filtered substances are selectively reabsorbed and secreted to maintain homeostasis in plasma. The kidneys have several endocrine functions: to produce renin which regulates blood pressure and blood volume through the renin-angiotensin-aldosterone system; to produce erythropoietin, which regulates the production of red blood cells; to activate vitamin D, which regulates calcium uptake and maintains bone health, and to produce endothelin, which affects glomerular pressure and inflammation and has an important role in modulating kidney function.

The glomerular filtration rate (GFR), representing the flow of plasma from the glomerulus into Bowman's space over a specified unit of time, is used to evaluate kidney function. About 25% of the blood volume delivered by the heart per minute, corresponding to approximately 1.2 litres of blood, flows through the capillaries per minute. Around 650 ml of renal plasma is filtered through the glomeruli per minute, producing circa 120 ml primary urine per minute. In total, the primary urine volume amounts to around 180 litres per day, which is then concentrated in the tubular system, resulting in approximately 1-2 litres of final urine per day.

A decline in kidney function leads to an accumulation of uraemic toxins, fluid overload, imbalances in the body's homeostasis, and hormonal disturbances. Patients experience increased symptom burden such as fatigue, poor mobility, muscle weakness, lack of physical and psychological stamina, anxiety, poor sleep, sexual dysfunction, itching, depression, decreased appetite and pain (1).

Chronic kidney disease

Definition, prevalence and aetiology

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health (2), and is classified based on three components: cause, estimated glomerular filtration rate (eGFR) and levels of albuminuria (A1-A3) (2). Albuminuria serves as an early indicator of nephropathy and independently predicts the risk of kidney failure, cardiovascular disease, and overall mortality, irrespective of eGFR (3). Each of the three components in the classification system plays a vital role in evaluating individuals with CKD, facilitating the determination of disease severity and associated risk (2).

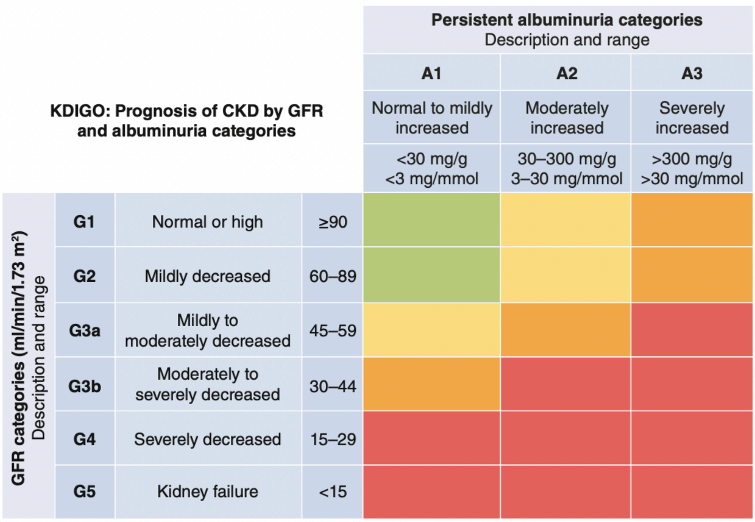

Figure 1. Prognosis of CKD by GFR and albuminuria categories
KDIGO staging system for chronic kidney disease (2). Green indicates a low risk (if no other markers of kidney disease, no CKD), Yellow indicates a moderatly increased risk, Orange indicates a high risk, Red indicates a very high risk. GFR, glomerual filtration rate. © 2023 Kidney Disease: Improving Global Outcomes (KDIGO). Published by Elsevier Inc. on behalf of the International Society of Nephrology. CC BY-NC-ND 4.0.

CKD is a global health problem with a prevalence of approximately 10% and is expected to be the fifth leading cause of death by 2040 (4). Population growth, ageing and the rising prevalence of diabetes, heart disease and hypertension are the primary factors contributing to the increasing prevalence of CKD, especially in economically advanced regions (5). CKD can affect individuals at any age, although it is most common in older people. Main causes of CKD include diabetes and hypertension. Other causes of CKD are primary glomerulonephritis, chronic tubulointerstitial nephritis, hereditary or polycystic kidney diseases, secondary glomerulonephritis, or vasculitis (6).

Comorbidities and mortality in CKD

Patients with CKD often present with a high burden of comorbid conditions including hypertension, cardiovascular disease, anaemia, diabetes mellitus, and thyroid disorders (7). Multiple comorbid conditions affect the treatment burden, medication management, quality of life, adverse outcomes and survival for these patients (7, 8).

Furthermore, patients with CKD have an increased risk of all-cause mortality, with cardiovascular complications as the leading cause of death (9). In the general population, low levels of physical activity are the fourth leading risk factor for mortality (10). In patients with CKD, low levels of physical activity and loss of muscle mass are associated with cardiovascular disease and increased mortality (11, 12). The decline in physical activity levels and a lower physical performance escalate an already increased risk of mortality in patients with CKD, emphasizing the importance of incorporating exercise and physical activity into standard care of patients with CKD.

Kidney replacement therapy

When patients reach kidney failure, defined by a GFR of less than 15 mL/min/1.73 m^2, it is necessary to plan for and eventually initiate kidney replacement therapy (KRT) to sustain life, either with maintenance dialysis or a kidney transplant (KT).

Dialysis removes waste products and excess fluid from the blood. Kidney failure that requires dialysis is associated with high mortality rates and reduced quality of life (13). This highlights the significance of preserving kidney function, in which physical activity is an important part of the lifestyle interventions included in preservative management strategies (14). There are two types of maintenance dialysis: haemodialysis (HD) and peritoneal dialysis (PD). In HD treatment, the blood is led out from the vascular system through a vascular access, filtered through a dialyzer with dialysis fluid which removes uraemic toxins and excess fluid, and restores acid-base and electrolyte balance, before it is returned to the bloodstream.

HD can be performed in-centre at hospital, at a dialysis clinic or at home, usually performed 3 times per week, for 4 hours each time. In PD, dialysis solute is infused into the abdominal cavity through a permanent catheter allowing toxins and excess water to be removed from the blood by using the peritoneum as a semi-permeable membrane. The dialysis solute is exchanged with regular intervals, either intermittently four times every 24 hours or continuously during the night for 10 hours by a machine. PD is home-based, continuous, and performed by the patients themselves or with assistance.

In kidney transplantation a donor kidney, from a living or deceased donor, is surgically inserted. This is the most preferred treatment option for kidney failure (15). Patients who have undergone KT have improved quality of life, reduced risk of cardiovascular events and increased survival rates compared to patients on maintenance dialysis (15).

Physical activity and physical performance in CKD

Physical activity can be defined as any bodily movement produced by the skeletal muscles that requires energy expenditure (16). Low levels of physical activity can be seen at all stages of CKD (17). As kidney function declines, patients experience a progressive loss of aerobic capacity, muscular strength, muscular endurance and balance (18, 19). This decline of physical performance is seen already in the early stages of CKD. It contributes to a downwards spiral where physical inactivity is attenuated by common symptoms of CKD such as fatigue, nausea and decreased appetite, resulting in further loss of physical performance that can affect activities in daily life.

Pathophysiological changes affecting physical performance in CKD

In CKD, many disease-related factors contribute to the loss of physical performance, such as increased muscular atrophy as well as decreased muscle protein synthesis and repair (20). A low calorie and protein intake, due to altered perception of taste and low appetite, can cause further loss of muscle mass. Furthermore, a dysregulation of appetite hormones and inflammatory cytokines can lead to a suppressed food intake that can exacerbate loss of muscle mass (20, 21). Aerobic capacity can be decreased, affected by impaired oxygen delivery due to decreased maximal heart rate, fluid overload, anaemia, fatigue and reduced endurance (22). This complex interaction of disease-related factors creates barriers to physical activity and exercise.

Metabolic acidosis

The kidneys have a central role in the regulation of the acid-base balance. When kidney function declines, the excretion of acid is reduced, hydrogen ions build up and levels of bicarbonate decrease, leading to metabolic acidosis. Metabolic acidosis increases muscle catabolism and is associated with bone mineral density loss and increased all-cause mortality in patients with CKD (23).

Inflammation

Low grade systemic inflammation is common in patients with CKD, contributing to increased muscular atrophy and is associated with increased all-cause mortality. Several factors contribute to chronic inflammation in CKD, such as an increased production of proinflammatory cytokines, oxidative stress, acidosis and infections (24).

Insulin resistance

Multiple factors cause insulin resistance in CKD, such as uraemic toxins, chronic inflammation, oxidative stress, vitamin D deficiency, metabolic acidosis, anaemia and physical inactivity (25). Insulin resistance is prevalent in diabetic as well as in non-diabetic patients with CKD. Disruption of the insulin signalling contributes to increased muscular atrophy (26) by increased protein catabolism and decreased protein synthesis (27).

Fluid overload

A decline in kidney function leads to an imbalance in the body's fluid homeostasis. Fluid overload increases cardiac load, increases blood pressure, leads to left ventricular hypertrophy, congestive heart failure and a higher risk of all-cause mortality (28). Fluid overload is common in patients with CKD, not on KRT, as well as in patients with kidney failure (29, 30). Typical symptoms are high blood pressure, oedema and shortness of breath. Fluid overload is associated with slower gait speed in patients with CKD (31) and higher risk of falls and hospitalization (32).

Renal anaemia

One of the most common complications in CKD is renal anaemia. The decline in kidney function leads to a decreased renal production of erythropoietin, iron dysregulation, chronic inflammation, and nutritional deficiencies (33). Common symptoms include fatigue, low energy, weakness, shortness of breath, dizziness, decreased exercise tolerance and impaired cognition. Anaemia is a key contributor to loss of exercise capacity and is associated with lower levels of physical activity, decreased physical performance and decreased quality of life in patients with CKD (31, 34). However, with the introduction of erythropoietin treatment, studies have shown significant improvements in physical performance (34) cognitive function (35) and quality of life (34, 36, 37).

Uraemic symptoms

The symptom burden in CKD is substantial (1, 38). As kidney disease progresses patients experience increasing uraemic symptoms. A global systematic review and meta-analysis showed that the prevalence of fatigue was 70% in patients with CKD 1-5 (1). Poor mobility was the second most prevalent symptom, followed by bone and joint pain, drowsiness and general pain, all reported in over 50% of the patients. More than 45 % of the patients reported poor sleep, sexual dysfunction, muscle cramps, itching, heartburn, dry skin and swelling in the legs (1). The symptom prevalence in patients on maintenance dialysis is similar to that reported in patients not on KRT. Fatigue was the most prevalent symptom reported in 70% of the patients on maintenance dialysis followed by muscle weakness, heartburn, weight loss, poor sleep, dry skin, poor mobility, muscle cramps, itching and trouble with memory reported in more than 50% of the patients. Although there are fewer studies reporting symptom prevalence in KT recipients, more than 50% of the patients in the included studies reported indigestion, abdominal pain, constipation, bone or joint pain, muscle weakness and muscle cramps (1). In the European QUALity study on treatment in advanced chronic kidney disease (EQUAL) study, symptom burden in patients aged 65 years and older was examined in six European countries. Results show that the symptom burden is higher among women compared to men (38).

Physical performance and evaluation of physical performance in CKD

Assessment of physical performance is used to identify patients who are at risk of sarcopenia and frailty and serves as a basis for prescribing and evaluating exercise interventions. There is a wide heterogeneity in instruments to evaluate physical performance in patients with CKD (39). Although physical performance can be assessed in laboratory settings, functional tests are more commonly used in clinical practice.

Aerobic endurance

Aerobic endurance is the body's ability to sustain prolonged physical activity using aerobic metabolism. Aerobic capacity is the ability to deliver oxygen to the muscles, and its uptake in muscle mitochondria, creating energy by producing adenosine triphosphate (ATP) during sustained physical activity (40).

During the initial force development, muscles use stored ATP, and energy derived from the breakdown of phosphocreatine (PCr). The ATP-PCr system is an anaerobic process, with rapid ATP resynthesis, lasting for the first 10 seconds of muscle activation. After the initial energy supply of ATP is depleted, the muscles proceed to create ATP through anaerobic glycolysis. In this anaerobic process, ATP is produced by the break-down of glucose or glycogen to pyruvate (40). When oxygen is limited, pyruvate is converted into lactate, leading to lactate accumulation which contributes to fatigue (41). When the energy demands can no longer be met by anaerobic glycolysis, the ATP synthesis shifts to aerobic oxidative phosphorylation within the mitochondria (40). After about six minutes of work, the oxidative system becomes the primary energy-producing system. When intensity is increased, there is an increase in lactate production. When the rate of lactate production exceeds the rate of lactate clearance during exercise of increasing intensity, the lactate threshold is reached, and anaerobic processes once again supplement energy production. To summarize, aerobic endurance depends both on maximal capacity and on when the lactate threshold occurs (40). To sustain prolonged work, it is necessary to avoid the accumulation of lactic acid.

The gold standard for measuring aerobic capacity is by measuring when maximal oxygen consumption, VO_2max, is reached during a maximal exercise test on a treadmill or cycle ergometer (40). While VO_2max in healthy individuals is limited by muscular oxygen uptake, oxygen carrying capacity in the blood and cardiac output, there are additional factors to consider in patients with CKD. One suggested limitation in VO_2max tests can be variability in individual effort, where patients with chronic disease and multiple comorbidities experience early onset of fatigue (42). Additionally, to reach VO_2max, the amount of muscle mass must be sufficient to be able to place maximal demand on both the cardiovascular and aerobic systems. In patients with CKD, decreased peripheral circulation and muscular limitations, anaemia, fluid overload and electrolyte imbalances, disturbed pH balance and unfamiliarity with exercise may result in an inability to reach maximal effort, affecting the accuracy and reproducibility of the test. Furthermore, patients with CKD have a high prevalence of cardiovascular disease (43) such as ischaemic heart disease and congestive heart failure that affect aerobic capacity. In clinical populations where patients cannot safely or physiologically reach VO_2max, VO_2peak, the highest oxygen uptake reached during an exercise test, is often preferred to evaluate cardiorespiratory fitness. However, physiological tests are time intensive, costly and technically complex, making them difficult to use in standard clinical care. An alternative is using functional, submaximal tests to indicate aerobic capacity or endurance ability. Submaximal tests can be used to assess functional limitations and to evaluate the outcome of exercise programmes. Submaximal tests are more appropriate to use in a clinical setting to evaluate and monitor physical performance as they are easy to perform, cost effective and reflect activities performed in daily life. Common functional tests used to assess aerobic endurance in CKD are the 6-minute walk test (6MWT) or the Incremental Shuttle Walk Test (ISWT) (39). Normal walking (5km/hour) requires an oxygen uptake of about one litre per minute, corresponding to approximately 50W on a cycle ergometer (44).

Balance

Postural control is defined as the act of maintaining, achieving or restoring a state of balance during any posture or activity. Postural control is a multifaceted process that depends on the coordinated function of several bodily systems: vestibular function, proprioceptive information from joint receptors, joint stability, Golgi tendon organs and muscle spindles in skeletal muscle, muscular strength and endurance and visual feedback. Strategies for postural control can be either predictive or reactive (45).

Clinical tests of balance assess different components of balance ability: static stability, underlying motor systems (strength, coordination), functional stability limits, verticality (ability to orient appropriately in respect to gravity), reactive postural control, anticipatory postural control, dynamic stability, sensory integration (ability to reevaluate sensory information when altered) or cognitive influences (46). Neural structures responsible for proprioception decline with age (47). Patients with CKD often have sensory and motor nerve dysfunction that can compromise balance, reaction time and muscular strength (48). Peripheral neuropathy is common in CKD, resulting in loss of sensation, weakness and pain, starting distally in the lower limbs and progressing proximally; with disease progression, similar symptoms can manifest in the upper limbs (49). Patients with CKD have a higher risk of falling compared to healthy individuals and falls in patients with CKD can result in fractures which are more common in patients with CKD due to impaired bone metabolism (50), highlighting the importance of evaluating balance in these patients. There are several functional tests of balance that are commonly used in patients with CKD such as the Berg balance scale (BBS), Short Physical Performance Battery (SPPB) and the Timed up and go (TUG) (39).

Muscular strength and endurance

Muscular strength is the ability to exert force in a muscular contraction (51), reflecting the muscle's neuromuscular and physiological functioning. The gold standard for measuring muscle strength is isokinetic dynamometry. In the clinical setting, muscle strength is commonly evaluated: by evaluating isometric strength, by establishing the one repetition maximum (RM) or by using submaximal tests with 3-10 RM to estimate the 1RM. Muscular endurance is the ability to perform repeated muscular contractions against a load over an extended period of time, either in one muscle or in a muscle group (51). Muscular endurance enables sustained activities over time, which is important in everyday life.

Skeletal muscle homeostasis relies on a balance between protein synthesis and degradation, ensuring maintenance of muscle mass and function. Muscle fibres in skeletal muscles are composed of thin and thick filaments, arranged in units known as sarcomeres, the basic contractile unit of the muscle. The muscle contraction and relaxation are contingent on the sliding of these filaments. The thin filament consists of the protein molecules actin, tropomyosin and troponin. The thick filament consists of the protein molecule myosin. In addition, there are several other proteins involved in the muscular contraction. There are different skeletal muscle fibres that have different shortening speeds and abilities to generate maximal force. Type 1 fibres have a high level of aerobic energy production, a high oxidative capacity and a slow contractile speed. Type 1 fibres are recruited during low intensity exercise and during daily activities such as walking and maintaining postural control. Type 2 fibres have an anaerobic process that generates more force compared to type 1 fibres, but with shorter time to fatigue. The type 2 fibres are categorized into type 2a (which combines aerobic and anaerobic processes) and type 2x fibres (which is purely anaerobic). Type 2a fibres have a moderately high oxidative capacity and a high glycolytic capacity, with a fast contractile speed. They are recruited for shorter high-intensity endurance exercise or resistance exercise with a high number of repetitions. Type 2x fibres have a low oxidative capacity, the highest glycolytic capacity and fastest contractile speed of the muscle fibres. They are recruited in explosive movements such as sprints and maximal strength lifts. Contraction of skeletal muscle consists of a progressive recruitment of muscle fibres depending on the activity that is being performed, starting with type 1 and continuing with type 2a and 2x as the intensity of the activity increases (40). In a study where muscle biopsies were obtained from patients with CKD 4-5, results showed that while the proportion of type 1 fibres were similar in patients with CKD compared with a healthy control group, the patients with CKD had significantly more type 2a fibres and significantly less type 2x fibres compared with the control group (52).

In healthy skeletal muscle metabolism, there is a variety of physiological processes. The mitochondria supply energy, producing ATP, as well as suppressing inflammation. Normal energy production produces low levels of reactive oxygen species (ROS). The muscle satellite cells promote muscle repair and muscle regeneration. Muscle synthesis depends on increased ribosomal biogenesis and translation of mRNA into new muscle proteins. Protein degradation via the ubiquitin-proteasome system (UPS) provides amino acids for muscle growth. To ensure that the nutrient intake supports normal cell functions and metabolism, appetite is regulated by hormones.

In CKD, these processes become dysfunctional, leading to muscle protein loss (20). Mitochondrial dysfunction leads to an inefficient energy production. An increase in mitochondrial permeability enables the release of cytochrome c, which leads to the activation of caspase 3 contributing to an accelerated breakdown of muscle protein. Mitochondrial dysfunction also leads to an increase of ROS, producing excessive oxidative stress and increased inflammation. Furthermore, muscle regeneration and muscle repair are decreased due to impaired insulin-like growth factor 1 (IGF1) signalling, reducing the activation of satellite cells. An impaired ribosomal biogenesis results in reduced protein synthesis, which in combination with increased muscle protein degradation causes excessive muscle atrophy. The appetite hormones become imbalanced resulting in reduced nutrient intake, which further affects the ability to promote normal cell metabolism (20).

In patients with CKD, increased muscular atrophy and fatiguability result in reduced muscular strength and muscular endurance. Decreased muscular strength in patients with CKD is associated with increased mortality (53).

Muscular strength in patients with CKD is often assessed in the clinical setting by measuring isometric strength across different muscle groups, or by evaluating overall muscle function. Hand grip strength (HGS) and quadriceps strength is commonly used to evaluate muscular strength in patients with CKD. Muscular endurance is evaluated by assessing the time that a static contraction can be performed or by assessing the number of dynamic contractions the muscle can produce. In patients with CKD, several tests are used to assess muscular endurance, reflecting functions essential for activities of daily living, such as different versions of the sit-to-stand (STS) test, toe and heel rises and biceps curls (39).

Fine motor skills

Fine motor skills, comprising force regulation and hand dexterity are important for performing activities in daily life. Motor and sensory capabilities of the hands deteriorate with age. In patients with CKD peripheral neuropathy, such as polyneuropathy or median nerve compression, can further affect the hand dexterity and fine motor skills (54, 55).

Exercise prescription

The increasing number of patients with CKD indicates a need for cost-effective, sustainable and self-administered exercise prescription. Although some studies with longer intervention periods have examined home-based exercise interventions, little is known about the best methods to prescribe and monitor self-administered exercise programmes in patients with CKD.

Exercise is a subcategory of physical activity, which is planned, structured and repetitive with the intention of maintaining or improving physical fitness or health (56). When prescribing exercise, physiotherapists follow the FITT-VP principle, an acronym for frequency, intensity, time, type, volume and progression (44). The FITT-VP principle needs to be adapted to each patient's individual response to exercise, their needs, limitations, and ability to exercise. Furthermore, the patient's goals and objectives need to be taken into consideration (44).

Exercise frequency

Exercise frequency refers to how often exercise should be performed, usually defined as number of sessions per week (44).

Exercise intensity

While exercise frequency, type and time can easily be quantified, assessing exercise intensity is more challenging. In *aerobic exercise*, exercise intensity can be prescribed by percentage of maximum oxygen uptake, percentage of heart rate maximum, percentage of heart rate reserve, lactate threshold, or with subjective measures such as rating of perceived exertion (RPE). In *resistance exercise,* intensity can be prescribed using the percentage of one RM, with the number of repetitions or with subjective exertion. However, quantifying exercise intensity – or levels of difficulty, for static and dynamic *balance exercise* is complex and there is a knowledge gap regarding the best methods of prescribing exercise intensity for balance exercise.

Borg Rating of Perceived Exertion scale

The Borg RPE scale (57) is a subjective scale, developed by Gunnar Borg in 1970 to evaluate perceived level of exertion after physical activity. The scale ranges from 6 – 20 and correlates with heart rate (table 1). Although the Borg scale was originally developed for young, healthy men, it is now widely applied in older adults and across various disease populations. While maximum heart rate declines with age, research indicates that the scale remains valid for estimating level of perceived exertion in older adults (58). This subjective measure can be influenced by multiple factors and provides an integrated assessment of overall effort.

The Borg RPE scale is primarily used to evaluate exertion during aerobic physical activity. In aerobic exercise, the amount of anaerobic work and the resulting lactic acid accumulation could affect a person's subjective experience of how strenuous the exercise is. The RPE scale is particularly valuable when heart rate measures of exercise intensity are inaccurate or attenuated, as in patients on beta blocker medication (59) or with autonomic neuropathy, which both are common in patients with CKD (60). This is due to the scale's ability to capture perceived exertion emanating from different sources: the cardiovascular, respiratory and central nervous systems (57).

The Borg RPE scale is often used to describe the level of exertion of aerobic exercise intensity in patients with CKD. In healthy individuals, the Borg RPE scale has been validated as a method evaluating exercise intensity in resistance exercise, where levels of exertion can be influenced by load, volume, proximity to failure, and lactate accumulation (61). However, no studies have evaluated the Borg RPE scale as an instrument to prescribe exercise intensity in patients with CKD, and no studies have evaluated the Borg scale as a method to prescribe and monitor balance exercise.

Table 1. The Borg Rating of Perceived Exertion scale, and corresponding levels of exercise intensity

RPE	Verbal anchors	Intensity
6	No exertion at all	Very light
7	Extremely light	
8		
9	Very light	Light
10		
11	Light	
12		Moderate
13	Somewhat hard	
14		Vigourous
15	Hard	
16		
17	Very hard	
18		Near maximal to maximal
19	Extremely hard	
20	Maximal exertion	
The table is based on the Borg RPE Scale® with the levels of intensity from ACSM Guidelines for Exercise Testing and Prescription (44)		

Exercise time

Exercise time describes the duration of each bout of exercise (time per session, time per day or time per week) (44).

Exercise type

Exercise type is chosen depending on the aim of the exercise intervention. Aerobic endurance exercise consists of activities where the body's large muscles move in a rhythmic manner, for a sustained period of time, improving cardiorespiratory fitness (16). Different modalities of aerobic endurance exercise include walking, running, swimming, and bicycling. Balance exercise comprises static and dynamic exercises designed to improve an individual's ability to withstand challenges from postural sway or destabilizing stimuli caused by self-motion, the environment, or other objects (16). Resistance exercise consists of exercises that increase skeletal muscle strength, power, endurance, and mass (16). Flexibility exercises aim to improve the movement through its full range of motion, and exercises are adapted to each specific joint and the surrounding ligaments and tendons (16).

Exercise volume and progression

Other factors to take into consideration when prescribing exercise are the total volume of exercise (the product of exercise frequency, intensity and time), and the importance of exercise progression over time. Exercise volume can be specified as metabolic equivalent (METs) minutes per week. Exercise can progress by modifying any of the FITT-VP components and needs to be adapted to the individual's response to exercise (40).

Exercise setting

Another important factor to consider is the setting in which exercise should be performed: at home, in-centre, at a gym, outdoors, supervised or self-administered (44). In-centre exercise may reduce risks when performing exercise and enables easy progression as well as increasing adherence to the exercise programme (44). However, it demands more resources, is less flexible and is dependent on the patient travelling to the exercise location compared to self-administered exercise. Self-administered exercise can be performed in a patient's home, at a gym, or outdoors, depending on the patient's preference. It can increase patient autonomy and is highly flexible regarding when the exercise is performed. However, there may be higher risks when performing self-administered exercise and exercise progression is more difficult to achieve compared to in-centre exercise.

Strategies to increase physical activity

There are several strategies for promoting behavioural change and increasing physical activity. The concept of self-efficacy is being confident that one can be successful in carrying out a certain task, like for instance exercise (44). Strategies to enhance self-efficacy for exercise include: providing instruction and demonstration of the exercise programme, setting realistic and achievable goals, self-monitoring and documenting exercise to track progress, have a progression of the exercise programme over time, watching others with a similar background perform exercise, receiving frequent feedback and encouragement and being able to communicate regarding the meaning of symptoms associated with the behavioural change (44).

Exploring and setting goals can be an important motivator to exercise, and it is important to set both short term and long term goals to increase self-efficacy (44). Preferably, goals should be specified according to the SMART criteria, standing for Specific, Measurable, Achievable, Realistic, and Timed (62).

Exercise recommendations

The World Health Organization (WHO) recommends that adults between 18-64 years of age should perform at least 150 minutes of moderate-intensity physical activity, or 75 minutes of vigorous-intensity physical activity, throughout the week, alternatively perform a combination of both. For additional health benefits, they recommend increasing the moderate-intensity physical activity to 300 minutes per week (16).

Muscle-strengthening activities involving major muscle groups should be performed two days per week or more (16).

Adults aged 65 years and above are recommended additional physical activity to improve balance and prevent falls, three days per week or more (16).

Exercise recommendations for patients with CKD are based on the general exercise recommendations from WHO (16). Kidney Disease Improving Global Outcomes (KDIGO) 2024 recommends that patients with CKD should undertake moderate intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible to their physical and cardiovascular tolerance (2). Further, they recommend that patients with CKD should avoid sedentary behaviour and that patients with a higher risk of falling should be advised on what type of exercise should be performed (aerobic vs. resistance, or both) and at what intensity the physical activity shall be performed (low, moderate, or vigorous) (2).

Risks, harms and challenges in exercise prescription for patients with CKD

Exercise prescription needs to be individualised to ensure safety while performing exercise by adapting the exercise frequency, intensity, type, time, volume and progression to the patient’s current health-status, physical performance and exercise tolerance.

Risks and harms

Common pathology in CKD can introduce risks during exercise. Before exercise is prescribed, comorbidities need to be evaluated, and potential risks and contraindications taken into consideration. In addition to contraindications to exercise listed in the American College of Sports Medicine (ACSM) guidelines for exercise testing and prescription (44) there are contraindications to exercise specific for patients with CKD; fluid imbalances, electrolyte imbalances such as hypo- or hyperkalaemia, cardiovascular instability, excess inter-dialytic weight gain, pulmonary congestion and peripheral oedema, or if the patient is unstable on dialysis treatment (63). For contraindications and risks for exercise in patients with CKD, see table 2.

There are potential harms if exercise is not adapted accordingly, such as musculoskeletal injuries, falls, hernia formation, mechanical kidney injury, damage to the vascular access or catheter site, hypoglycaemia, and cardiovascular events (44, 63, 64).

However, studies have shown that exercise interventions in patients with CKD are safe to perform both supervised and self-administered (65-67). There are few studies reporting adverse events related to exercise interventions. The most commonly reported event is hypotension. There have also been reports of knee pain, rapid atrial fibrillation, Achilles tendon pain, joint pain, and chest pain (22).

Challenges

Patients with CKD face a myriad of symptoms, with fatigue being the most reported barrier to exercise in patients with CKD (68). Lack of advice and support from the nephrologist and other kidney staff is an important barrier to performing exercise, while support from health-care professionals, family and friends is a facilitator (69). Inactivity, no or little previous exercise experience and uncertainty of how to perform exercise is also reported to be a barrier. By individualizing the exercise prescription according to each patient's needs, motivators and goals, many of the challenges to performing regular exercise can be overcome.

Table 2. Contraindications and risks for exercise in patients with CKD

Category	Patients	Description	Recommendations for exercise
Absolute contraindications[1]	CKD- all stages	Uncontrolled medical condition (clinically unstable) including (but not limited to) infection or fever, recent (within 2 weeks) myocardial infarction or undiagnosed chest pain[1] Unstable ischaemia[1] Decompensated heart failure[1] Uncontrolled arrhythmias[1] Severe and symptomatic aortic stenosis[1] Hypertrophic cardiomyopathy or cardiomyopathy from recent myocarditis[1] Severe pulmonary hypertension[1] Symptomatic hyper- or hypotension[1] Perceived physical or psychological barriers to exercise participation[1] Other conditions that could be aggravated by exercise (resting systolic blood pressure >200 mm Hg or resting diastolic blood pressure >110 mm Hg; active or suspected myocarditis or pericarditis; Suspected or known dissecting aorta aneurysm; Thrombophlebitis and recent systemic or pulmonary embolus)[1] Severe anaemia Severe hypo/hypercalcaemia Severe hypo/hyperkalaemia Severe metabolic acidosis Pulmonary congestion Inability to understand instructions Severe hypo/hyperglycaemia	Exercise should not be performed
	HD	Exessive interdialytic weight gain with severe predialytic overhydration and/or intradialytic or postdialytic hypotension	

Relative contraindications	CKD – all stages	Electrolyte imbalances Moderate hypo/hyperkalaemia Moderate hypo/hypercalcaemia	After approval from the nephrologist, adapted exercise may be performed with a lower exercise intensity.
		Moderate symtomatic fluid overload	After approval from the nephrologist, adapted exercise may be performed with a lower exercise intensity to avoid exessive strain on the cardiovascular system.
		Severe anaemia and concomittent artheriosclerotic heart disease	After approval from the nephrologist, adapted exercise may be performed with a lower exercise intensity.
Risks	CKD – all stages	Increased risk of tendinitis	Precede exercise sessions with warm-up period. Gradully increase exercise intensity and duration.
	Polycystic kidney disease	Increased risk of mechanical kidney injuries and hernia formation	Individualised exercise programmes avoiding exercises that increase the intra-abdominal pressure such as jumping and abdominal crunches, depending on the patients tolerence. Avoid contact sports.
	HD	Risk of haemodynamic instability[1]	Avoid intra-dialytic exercise the first 30 minutes of HD treatment
	Vascular access	Risk of damage to access site	Avoid exercise that cut off blood flow in the limb with the vascular access. Avoid blood pressure monitoring on the limb with the vascular access. Avoid performing exercise after recent vascular surgery/intervention (no exercise involving the limb with temporary or healing fistula)
	Central venous catheter	Risk of infection	Activities with water submersion (swimming/bathing) are contraindicated.
		Risk of dislocation	Avoid exercises that increase risk of dislocation and cause discomfort
	PD	Increased risk of hernia formation	Moderate to high intensity exercise should be performed without or with little dialysate in the abdomen to avoid discomfort and minimize risk of hernias. Low intensity exercise can be performed with dialysate.
		Risk of mechanical injury to the access site	Avoid exercises that can cause mechanical injury to the acccess such as exercises in prone position.
		Increased risk of infection at catheter site	The catheter site should be properly covered to avoid infection when performing aquagym, swimming or bathing.

	KT	Risks of post-operative complications (wound dehiscence, incisional hernia)	During the first 2 months post-operative: Avoid activities that cause pain or discomfort in the surgical area (abdomen).
		Increased risk of damage or ruptur of the achilles tendon due to high levels of steriod medication the first months after KT	During the first 3-6 months post-operative: Avoid activities that put extra strain on the achilles tendon such as exessive walking, jumping, running, or other activities that comprise rapid stretching of the tendon. Increase exercise duration progressivly.
		Risk of damage to the transplanted kidney[1]	Avoid contact sports. Use appropriate orthotic kidney guard while performing sports with risk for accindental impact. Prolonged extreme exercise should be carefully considered.

Note: For conditions listed as absolute contraindications, exercise should not be performed until the underlying condition is treated when possible. For conditions listed as relative contraindications, it is almost always possible to perform some sort of exercise as long as the exercise dose is adapted and the underlying condition is treated when possible. HD: hemodialysis, PD: peritonal dialysis, KT: kidney transplant.
[1]Contraindications established in the British Renal Association's Clinical Practice Guideline (64). Other contraindications and risks are based on clinical experience and risk assessment and considered clinically relevant. In general research evidence is limited or unavailable.

Exercise in clinical practice for patients with CKD

At Skåne University Hospital in Lund, Sweden, evaluating physical performance and prescribing exercise in patients on maintenance dialysis was implemented in clinical routine in the 1990s. The physiotherapists at the kidney department compiled a set of tests to evaluate aerobic endurance, balance, muscular strength, muscular endurance and fine motor skills (70). The test-battery includes stair climbing capacity, functional reach, hand grip strength, isometric quadriceps strength, toe rises, heel rises and the Moberg pick up test. It has been used regularly in clinical practice since the 1990s. The Kidney Departments at Skåne University Hospital consist of multidisciplinary teams, including nephrologists, kidney failure nurses, physiotherapists, nutritionists and medical social workers. The team's overarching aim is to provide a holistic and person-centred treatment. Over recent decades the physiotherapy unit at the kidney department has continued to evolve, introducing exercise as part of standard care for patients with CKD 3-5 and on KRT.

However, Sweden is one of few countries that have physiotherapists connected to most kidney departments (71) and resources vary between hospitals. In Sweden, physiotherapist appointments and in-centre exercise sessions are charged up to the threshold of the healthcare high-cost protection of 1450 Swedish kronor (approximately 137 euros) per year. Visits to other health-care professionals are included in this high-cost protection. In consequence, most patients with CKD reach this threshold quickly, enabling them to participate in exercise programmes without any additional cost.

At the Kidney Department at Skåne University Hospital, patients with CKD are offered individualised exercise programmes, performed in-centre or self-administered. For patients on HD, exercise is offered mainly before dialysis or on non-dialysis days, but there is also an option of intra-dialytic exercise according to the patient's preference. While most studies in patients with CKD have focused on in-centre exercise interventions, self-administered exercise or digital exercise solutions can make exercise more widely accessible, especially for patients in earlier stages of CKD, patients on PD and KT recipients.

Exercise studies in CKD

Historic perspective

The first studies of exercise in patients with CKD were published in the 1970s and 1980s when early proponents of exercise examined its effects on physical performance, coronary risk factors (72), metabolic, psychological and haemodynamic imbalances (73-75) and hypertension (76) in patients on HD treatment. In patients with CKD not on KRT, Clyne et al. showed that the progression of kidney disease decreased exercise capacity (77). The first study examining exercise in patients with CKD not on KRT was performed by Clyne et al. where the exercise group significantly improved work capacity as well as muscular strength and endurance in the lower extremities after 3 months of exercise compared with a sedentary control group (78). A study by Heiwe et al. showed that elderly patients with CKD significantly improved muscular strength and dynamic endurance, walking capacity, and functional mobility to the same extent as a healthy exercise group after 12 weeks of exercise compared with sedentary CKD and healthy control groups, respectively during the observation period of 12 weeks (79).

Since the pioneering studies, there has been a steady increase in published research on the effects of exercise in patients with CKD. In 2011 Heiwe and Jacobson published a meta-analysis for the Cochrane Collaboration comprising patients in all stages of CKD (80), which was updated in 2014 (18). However, few studies comprised patients with CKD, not on KRT. This meta-analysis showed significant effects of different exercise interventions on physical performance, walking capacity, cardiovascular function and HRQOL, with the strongest evidence for aerobic exercise interventions (18, 80).

Patients with CKD not on KRT

Although most studies have focused on patients undergoing maintenance dialysis, there are several meta-analyses on the effects of exercise on physical performance for patients with CKD not on KRT (81-85) as well as three meta-analyses comprising patients with CKD 2-5D (67, 86, 87) that have been published after the Cochrane report. However, these meta-analyses collectively cite 27 trials examining exercise effects on physical performance in patients with CKD not on KRT, and there is still a lack of large randomised controlled trials in these patients.

Exercise frequency, intensity time and type

The exercise interventions in the meta-analyses were performed 3-7 times per week with 3 times per week being the most common frequency (67, 81-87). The majority of the exercise interventions were performed at a moderate intensity, with one trial performing low to moderate intensity exercise (88) and two studies performing moderate to high intensity exercise (89, 90). Exercise sessions in the meta-analyses range from 10 to 90 minutes, and the most common duration was 30 minutes per session. The length of the exercise interventions in the included studies ranged from 5-78 weeks. Most trials have examined aerobic or resistance exercise or combined aerobic and resistance exercise interventions (67, 81-87). Evidence remains limited regarding the effects of other exercise modalities such as balance or flexibility exercise.

Setting

Most of the exercise trials were performed in-centre, with some studies performing in-centre exercise initially, and then transitioning into self-administered exercise (81-85). Five trials were performed self-administered (88, 91-94).

RCTs with intervention periods ≥ 6 months

Eleven studies included in the meta-analyses had intervention periods of 24 weeks or more (66, 91, 94-102). However, most of the studies with longer intervention periods had small sample sizes, apart from the trial by Weiner et al. (66) and the LANDMARK (Longitudinal Assessment of Numerous Discrete Modifications of Atherosclerotic Risk Factors in Kidney Disease) 3 trial (65, 95).

The trial with the longest intervention period was conducted by Eidemak et al. randomising 30 patients to 78 weeks of exercise or standard care. Aerobic exercise was performed self-administered, with a moderate intensity and a duration of 30 minutes per day. Work capacity increased significantly in the exercise group compared with the control group (94).

Weiner et al. randomised 99 patients to 12 months aerobic and resistance exercise or to a health-education control group. During the initial six months, exercise was performed in-centre three times per week. After six months, patients could choose to perform one of the three exercise sessions self-administered for the remaining six months of the study. The authors found that aerobic capacity improved in the exercise group compared with the control group at 6 months, but this improvement was not sustained at 12 months. The 6MWT was significantly improved in the exercise group both at 6 months and 12 months. The control group showed significantly worse results in the TUG compared with the exercise group. There were no differences between groups in the SPPB over time. The authors showed that their exercise intervention was safe and feasible. However, Weiner et al. did not reach their planned sample size of 120 patients and had a higher-than-expected drop-out rate and patients lost to follow up, resulting in 30 patients in the exercise group and 38 patients in the control group included in the analysis (66).

The LANDMARK-3 trial randomised 83 patients to 12 months of moderate intensity aerobic and resistance exercise or standard care. The exercise sessions were performed in-centre the first 8 weeks before transitioning to 10 months self-administered exercise at a duration of 150 minutes per week. There was an 11% increase in VO_2peak in the exercise group compared to a 1% increase in the control group (95). Results showed a 33% increase in METs in the exercise group and a 2 % decrease in the control group. Walking distance measured with the 6MWT improved significantly in the exercise group, both at 6 months and 12 months. Results for TUG were unchanged in the exercise group, but there was a decline in the control group. There was no effect on hand grip strength in either group. The LANDMARK trial reported a 70% adherence rate during the in-centre exercise period of 8 weeks, but adherence declined during the 10 months of self-administered exercise (65).

Leehey et al. randomised 36 patients to 12 months aerobic and resistance exercise and diet management or to diet management alone. Exercise was performed three times per week the initial 12 weeks of the study and then transitioned to self-administered exercise for the remaining 40 weeks, with in-centre follow up performed once per month. Results showed that the exercise group significantly improved in symptom-limited and constant-workout rate treadmill times at 12 weeks, but found no difference between groups at 52 weeks, and there was no difference between groups in the 6MWT, TUG or quadriceps endurance (102).

Hiraki et al. randomised 36 patients to 12 months of self-administered aerobic and resistance exercise or to a control group. Aerobic exercise was performed daily (30 minutes or 8000-10000 steps per day), and resistance exercise was performed three times per week with a hand grip strengthening device, as well as exercises to improve strength in the lower extremities. HGS and quadriceps strength improved significantly in the exercise group after 12 months of exercise compared with the control group (91).

In a pilot study by Greenwood et al. 20 patients were randomised to 12 months of combined aerobic and resistance exercise, performed three times per week in-centre at a vigorous intensity, resulting in significant improvements in relative VO_2peak in the exercise group compared with the control group but no difference in absolute VO_2peak (96).

In a pilot study by Mustata et al. 20 patients were randomised to 12 months of aerobic exercise or to a control group. The exercise was performed in-centre two times per week, and during the second month of the study patients performed additional self-administered walking exercise, starting with one time per week and progressing to three times per week. Exercise was performed with a moderate intensity and duration was increased progressively. Significant improvements in VO_2peak were seen in the exercise group compared with the control group (97).

Headley et al. randomised 21 patients to 48 weeks of moderate intensity exercise performed 3 days per week or standard care. Aerobic exercise was performed in-centre at a moderate intensity, 3 days per week. From week 24-48 the patients could also perform resistance exercise 2 times per week. VO_2peak was significantly increased in the exercise group compared with the control group (98).

Thompson et al. randomised 44 patients to 24 weeks aerobic and resistance exercise or to standard care. Exercise was performed with a moderate intensity. The first eight weeks exercise was performed in-centre one time per week and self-administered two times per week. During the following 16 weeks exercise was performed self-administered. The exercise group showed significant improvements in VO_2peak after eight weeks of exercise compared with the control group, but there was no significant between-group difference at 24 weeks (101).

Aoike et al. randomised 40 patients to 24 weeks of self-administered aerobic exercise, in-centre aerobic exercise, or to a sedentary control group. Exercise was performed with a mild to moderate intensity, three times per week. The results showed that VO_2peak, 6MWT, 2-minute step test and arm curl test significantly improved in both exercise groups and were unchanged in the control group (99).

In a pilot study by Leehey et al. 20 patients were randomised to 24 weeks of exercise or to a control group. The first 6 weeks were performed in-centre, followed by 18 weeks of self-administered exercise. Aerobic exercise was performed three times per week, with an exercise programme ranging from light to hard intensity. The home-based exercise consisted of walking. Results showed an increase in exercise duration during treadmill testing in the exercise group, but no significant between-group differences were found (100).

Number of included patients

Most of the exercise trials comprising patients with CKD not on KRT include less than 50 patients. The previously described studies by Weiner et al. (66) and the LANDMARK trial (65, 95) comprised samples with more than 50 randomised patients. Barcellos et al. randomised 150 patients to 16 weeks of combined aerobic and resistance exercise or to standard care, showing significant improvements in the 30 second STS (STS30) and the 2-minute step test in the exercise group compared with the control group (103). A study by Rossi et al. randomised 107 patients to 12 weeks of combined aerobic and resistance exercise or to standard care, showing significant improvements in walking distance measured with the 6MWT and muscular endurance with 10-times STS in the exercise group compared with the control group (104).

Exercise effects on aerobic capacity in patients with CKD not on KRT

Aerobic capacity, measured with VO_2peak was found to be significantly improved in several meta-analyses after aerobic or combined aerobic and resistance exercise interventions in patients with CKD not on KRT (81-84, 86) with the exception of the meta-analysis by Wu et al. (85). The intervention time of the included studies ranged from 5-78 weeks (81-84, 86).

Walking capacity, measured with the 6MWT was examined in five meta-analyses. Walking distance was significantly improvement compared with the control group after both in-centre and self-administered aerobic exercise, combined aerobic and resistance exercise (67, 82, 83) or resistance exercise (87). Junqué-Jiménez et al. found that although 6MWT significantly improved after self-administered exercise, the improvement was of small clinical relevance (less than 10% of change in walking distance), suggesting that the lack of supervision may contribute to the small change in walking distance (67). Pei et al. (86) found no difference in 6MWT between aerobic exercise and the control group. However, Pei et al. found that patients with CKD not on KRT had greater effects on walking distance, but only two trials comprising patients not on KRT were included in their analysis (86).

Aerobic endurance, measured with the 2-minute step test was found significantly improved in the meta-analysis by Traise et al. (82).

Exercise effects on muscular strength and endurance

HGS was found to be significantly improved in the meta-analysis by Chen et al. comprising seven trials including HGS as an outcome in patients with CKD 2-5D (87). The remaining two meta-analyses, based on two and seven trials, respectively, did not report a significant effect on HGS (67, 82).

Quadriceps strength was found to be unchanged in three meta-analyses (67, 81, 83). However, only four of the included trials evaluated quadriceps strength as an outcome. Three included trials reported significant improvements of quadriceps strength that were not observed in the control groups (91, 105, 106).

Significant improvements in muscular strength and endurance of the lower limbs measured with STS tests were found in two meta-analyses (67, 82).

One meta-analysis found significant improvements in maximal biceps-curl repetitions (83).

Exercise effects on balance

Three meta-analyses found significant effects on TUG after aerobic or combined aerobic and resistance exercise interventions performed both in-centre and self-administered (67, 81, 82). No other measures of balance were included as an outcome measure in the current meta-analyses.

Patients on maintenance dialysis

Most exercise trials for patients on maintenance dialysis comprise patients on HD. In the Cochrane report by Heiwe et al. 33 studies comprised patients on maintenance dialysis (80). In an updated Cochrane review of exercise effects in patients on maintenance dialysis by Bernier-Jean et al., published in 2022, an additional 56 studies were included resulting in a total of 89 studies (107). Of the included studies, 65 studies reported the effects of exercise on physical performance. Three of the included studies included patients on PD, four studies included patients on PD and on HD, and the remaining studies included patients on HD (107). One meta-analysis comparing exercise interventions with standard care comprising patients on PD has been published (108), including nine RCTs, of which six studies evaluated physical performance.

Exercise frequency intensity, time and type

The most common exercise frequency in the studies included in the Cochrane report was 3 exercise sessions per week, with a range of 2-5 sessions per week. Most of the included studies were performed with a moderate exercise intensity, five studies were performed with light to moderate exercise intensity, and nine studies with moderate to hard exercise intensity (107). The reported duration for the studies included in the Cochrane report was between 10 and 90 minutes per exercise session, while the majority of sessions were between 20 and 40 minutes. The exercise interventions lasted between 8 and 104 weeks. Of the studies included in the Cochrane report, aerobic exercise was examined in 56 studies. Resistance exercise was examined in 21 studies. Combined aerobic and resistance exercise was examined in 19 studies. Three studies examined flexibility exercise, and one study examined yoga (107).

In the meta-analysis examining exercise in patients on PD, the most common exercise frequency in the included studies was 3 exercise sessions per week, with a range of 3-5 sessions per week. Most of the included studies were performed with low intensity or low to moderate exercise intensity. The reported duration of the studies included were between 20-60 minutes per session, while the majority of the sessions were 30 minutes. The exercise interventions lasted between 12 and 24 weeks. Aerobic exercise was examined in one study, combined aerobic and resistance exercise was examined in four studies and Baduanjin movement was examined in one study (108).

Setting

In the Cochrane report from 2022, exercise was performed intradialytically in most studies (n=65). In seven of the included studies exercise was performed self-administered (107).

RCTs with intervention periods ≥ 6 months

In the Cochrane report, 23 studies had an intervention period of 24 weeks or more (107). Of these studies, five studies had an exercise intervention of 52 weeks or more (107).

In the meta-analysis comprising patients on PD, two studies had an intervention period of 24 weeks (108).

Number of included patients

Of the studies examining physical performance in the Cochrane report, 31 studies included more than 40 patients (107). The largest included study in the Cochrane report, the Exercise Introduction to Enhance Performance in Dialysis (EXCITE) trial comprised 296 patients on HD or PD. The EXCITE trial examined a self-administered walking exercise intervention during a 6-month observation period, resulting in significant improvements in walking distance measured with the 6MWT and significantly improved muscular strength measured with the 5 times STS test (109).

Of the studies examining physical performance in the meta-analysis for patients on PD, three studies included more than 40 patients.

The Dialysis Training Therapy (DiaTT) trial, published in 2023 and therefore not included in the 2022 Cochrane report, comprised 1211 patients on HD making it the largest exercise trial to date in patients on maintenance dialysis. The patients were randomised to 12 months, intradialytic, combined endurance and resistance exercise or to standard care. Results showed improved muscular endurance, balance and walking capacity in the exercise group compared with the control group (110).

Effects on aerobic capacity

In the Cochrane report VO_2max or VO_2peak was evaluated in 14 studies showing a significant effect on VO_2max or VO_2peak in the exercise groups.

Walking capacity measured with the 6MWT was evaluated in 19 studies with a significant effect on walking distance in the exercise groups (107).

The meta-analysis for patients on PD included two studies which examined walking distance and did not show a significant improvement in the exercise groups (108).

The DiaTT trial showed a significant improvement of 37.5 meters in the 6MWT in the exercise group compared with the control group (110).

Effects on muscular strength and muscular endurance

HGS was examined in ten studies, and exercise interventions showed a significant effect in the exercise groups (107).

Quadriceps strength was examined in eight studies, and exercise interventions showed a significant effect in the exercise groups (107).

Muscular strength and endurance evaluated with different versions of the STS test was examined in 16 studies. Exercise training of any type was likely to improve the 30- or 60- second STS test. Aerobic exercise interventions improved the 5 times STS and the 10 times STS (107).

The meta-analysis for patients on PD included three studies that examined HGS, with no significant effect of exercise (108). Two studies examined outcomes in STS30, one study found significant improvements after exercise while the other study found no significant difference. Two studies examined the 5 times STS, with one reporting significant improvements after exercise (108).

The DiaTT trial showed a significant improvement in the 60 second STS test in the exercise group and a significant decline in the group who received standard care after 12 months (110).

Effects on balance

TUG was examined in six studies, showing a significant reduction in TUG time for the exercise groups (107).

The DiaTT-trial showed significant reduction in TUG time in the exercise group compared with the control group (110).

Kidney transplant recipients

Exercise is recommended post-transplant but the evidence for health benefits in this population remains limited. In a systematic review and meta-analysis published in 2025, 23 RCTs were included, of which 15 examined exercise effects on physical performance (111).

Exercise frequency, intensity, time and type

Frequency for the exercise sessions were 2-7 sessions per week. Most of the studies performed exercise with a moderate to hard exercise intensity. Exercise duration ranged from 20 to 90 minutes per session. Three studies examined aerobic exercise, three studies examined resistance exercise, and nine studies examined combined aerobic and resistance exercise (111).

Setting

In three studies exercise was performed self-administered, five studies had a combination of in-centre and self-administered exercise, and the remaining studies were performed in-centre (111).

Effects on aerobic capacity

VO_2peak was examined in eight studies. Meta-analysis showed a significant increase in VO_2peak in the exercise groups (111).

Walking capacity measured with the 6MWT was examined in five studies. Two of five studies found favourable effects on walking distance, but it was not possible to perform a meta-analysis due to heterogeneity (111).

Effects on muscular strength and muscular endurance

Eight studies reported effects on muscular strength, six of eight studies favoured the intervention but there was no evidence that exercise had a favourable effect on muscular strength (111).

Hand grip strength was examined in three studies. Meta-analysis showed no significant effect of exercise on hand grip strength (111).

Muscular endurance assessed with the 60 second STS was examined in two studies. Meta-analysis showed a significant increase in the 60 second STS in the exercise groups (111).

Health-related quality of life in chronic kidney disease

The concept of health-related quality of life (HRQOL) is multidimensional, and is based on how people perceive their health reflected through physical capabilities, psychological function and social function (112). In addition, HRQOL includes assessment of the patient's level of satisfaction with treatment, outcome, and health status, also considering the patient's perspective of future prospects.

There is increasing awareness of the importance of assessing HRQOL as an indicator of well-being in patients with CKD, especially as medical advances are leading to increased life expectancy, meaning that patients with CKD live longer with the physical, mental and social challenges associated with the disease (113). Thus, there is a growing interest in evaluating Patient Reported Outcome Measures (PROMs), providing insight into the experienced well-being of patients (114). Healthspan has emerged as an important concept, which describes the years of life that are lived in good health, focusing on physical, cognitive, and mental well-being and quality of life (115).

Patients at all stages of CKD experience reduced HRQOL and increased symptom burden compared to healthy individuals and especially patients on maintenance dialysis (1). HRQOL is increased after KT compared to HRQOL in patients on maintenance dialysis and is slightly better compared to patients with CKD 3-5. However, HRQOL in KT is reduced compared to healthy individuals (1, 116). HRQOL is influenced not only by the severity of CKD, but also by therapeutic interventions, particularly maintenance dialysis, and by the range of symptoms that evolve as the disease progresses (1). From the perspective of patients with CKD, outcomes such as HRQOL and symptom management are often valued more highly than clinical measures such as survival (117, 118).

Evaluating health-related quality of life in patients with CKD

HRQOL can be evaluated using validated, self-administered questionnaires (PROMs). There is currently no consensus on the most appropriate instrument to use for evaluating HRQOL in patients with CKD. Both generic measures such as The Medical Outcomes Study Short Form 36 (SF-36), the 12-Item Short Form Health Survey, the WHO-Quality of life -BREF, the EuroQol-5d, the Hospital Anxiety and Depression scale, as well as disease specific measures such as different versions of the Kidney Disease Quality Of Life (KDQOL) questionnaire (119) are commonly used in patients with CKD (1).

Effects of exercise on health-related quality of life in CKD

CKD, not on KRT

In patients with CKD, not on KRT, meta-analyses have shown that depression improved significantly after aerobic or aerobic and resistance exercise interventions (120, 121), as well as other aspects of HRQOL measured with SF-36 (67, 82, 86). The Kidney Beam trial, including patients with CKD stages 2-5D, showed that a 12-week physical activity digital health intervention, resulted in significant improvements in the Mental component, evaluated with KDQOL-Short Form (SF) (122). However, Kidney Beam was not included in the meta-analyses above. Further research on exercise effects on HRQOL in patients with CKD not on KRT are needed.

Maintenance dialysis

In the Cochrane report from 2022, results showed that current exercise studies provide uncertain evidence regarding their impact on HRQOL in patients on maintenance dialysis. SF-36 was used for assessing HRQOL in 64 studies and 13 studies used a version of the KDQOL questionnaires (107). However, in a recently published meta-analysis that included an additional seven studies, there was a significant effect of aerobic and resistance exercise at a moderate intensity on both mental and physical component summary scores for patients on maintenance dialysis (123). Exercise could be performed both intra- and interdialytically, and supervised exercise was favoured. All included studies except one comprised patients on HD (124).

The to date, largest exercise trial in patients on HD, the DiaTT trial (110) was not included in the meta-analyses above. The DiaTT trial showed significantly improved physical component summary score and vitality subscales, evaluated with the 36-item Short Form Health Survey in the exercise group, while other subscales were unchanged (110). Another major study, the EXCITE trial (109), examined self-administered exercise in patients on HD and PD with KDQOL-SF, demonstrating a significant improvement in cognitive function score and quality of social interaction score in the exercise group compared with the control group. The other subscales were unchanged (109). The EXCITE-trial was included in the Cochrane report (107), but not in the most recent meta-analysis by Traise et al. (123).

Kidney transplant recipients

In the meta-analysis by Billany et al., seven studies examined HRQOL with SF-36. Three of seven studies favoured the exercise intervention with significant improvement in SF-36, but meta-analysis was not performed due to heterogeneity (111). Eight other studies assessed HRQOL with several different PROMs.

Rationale

CKD is associated with reduced physical performance and HRQOL. Although evidence is growing regarding the benefits of exercise for patients with CKD, there are few studies examining self-administered, individualised, long-term exercise programmes in patients with CKD 3-5. The RENal EXerCise trial was designed to include patients reflecting clinical settings, and the exercise intervention was designed to be feasible, integrating exercise into the routine of everyday life in the long-term. This thesis originates from the knowledge gap of whether self-administered exercise in patients with CKD was sustainable, safe, and efficacious and the effects of different types of exercise on physical performance and HRQOL. Specifically investigating whether the Borg Rating of Perceived Exertion scale could be used to prescribe and monitor self-administered aerobic endurance, balance and resistance exercise in patients with CKD, and the exercise programmes effect on physical performance and HRQOL.

Aims

The overall aims of this thesis were to investigate the effects of 12 months of self-administered, individualised exercise on physical performance and health-related quality of life and how to ensure safety, adherence and efficaciousness using the Borg scale to prescribe and monitor exercise in patients with CKD 3-5.

Specific aims

Paper 1

To compare the effects of 12 months self-administered balance or resistance exercise, both combined with aerobic endurance exercise, on physical performance.

Paper 2

To compare the effects of 12 months self-administered balance or resistance exercise, both combined with aerobic endurance exercise, on HRQOL.

Paper 3

To examine safety, adherence and performance during 12 months of self-administered aerobic endurance exercise, prescribed and monitored with the Borg RPE scale, and the relationships between exercise intensity and duration and change in aerobic endurance.

Paper 4

To examine safety, adherence and performance during 12 months of self-administered balance or resistance exercise, prescribed and monitored with the Borg RPE scale, and the relationships between exercise intensity and duration and change in balance or strength.

Methods and Patients

The RENal EXerCise trial

All papers in this thesis are based on the RENal EXerCise (RENEXC) trial, a head-to-head RCT, comparing balance and resistance exercise, both combined with aerobic endurance exercise, in patients with CKD 3-5. The RENEXC-trial was designed in 2010 by Naomi Clyne, Matthias Hellberg, Huda Abdulahi and Peter Höglund. The trial was conducted between October 2011 and May 2017, screening 217 patients and including 151 patients. Assessment of physical performance, prescription and monitoring of the exercise programmes and continuous follow up was performed by a dedicated research physiotherapist.

Study design

This thesis is based on four studies within the RENEXC-trial, a single-centre RCT comprising patients with CKD 3-5, not on KRT. Paper 1 reports the primary aims of the RENEXC-trial. Paper 2 is a pre-specified sub study of the RENEXC-trial. Papers 1 and 2 include all randomised patients and are analysed using intention to treat. Papers 3 and 4 are post hoc analyses with subgroups of the RENEXC-trial and are analysed per protocol. Paper 3 pooled all participants into one cohort, while Paper 4 analysed data with the original RCT design. An overview of the study design, participants, data collection and data analyses are seen in table 3.

Table 3. Overview of study design, participants, data collection and data analysis

Paper	1	2	3	4
Study design	Randomised controlled trial. Primary outcome.	Randomised controlled trial. Pre-specified substudy.	Pooled analysis of RCT data. Post hoc analysis.	Randomised controlled trial. Post hoc analysis.
Participants	All patients in RENEXC, n= 151	All patients in RENEXC, n= 151	Subgroup of RENEXC, n= 147	Subgroup of RENEXC, n= 148
Data collection	Assessment of physical performance at baseline and after 4,8 and 12 months of exercise	Assessment of HRQOL at baseline and after 4,8 and 12 months of exercise	Assessment of aerobic endurance at baseline and after 4,8 and 12 months of exercise	Assessment of balance and strength measures at baseline and after 12 months of exercise
Data analysis	Descriptive statistics. Mixed model analysis. Intention to treat.	Descriptive statistics. Mixed model analysis. Intention to treat.	Descriptive statistics. Student's paired *t*-test. Single and multiple linear regression analysis. Per protocol.	Descriptive statistics. Student's paired *t*-test or Wilcoxon signed-rank test. Student's independent *t*-test. Single and multiple linear regression analysis. Per protocol.

Patients

Study recruitment

Patients were consecutively recruited from the outpatient clinic at the Kidney Department at Skåne University Hospital in Lund, Sweden between October 2011 and May 2016. All prevalent and incident patients were asked if they were interested in participation and then screened by the nephrologist (MH), according to the inclusion and exclusion criteria.

Inclusion criteria

To reflect clinical reality, inclusion criteria were kept as open as possible. Adults ≥18 years of age, with an eGFR <30mL.min/1.73m^2 and with no contraindications to exercise were invited to participate in the study. Comorbid burdens were accepted to achieve a representative CKD study population, provided they did not constitute a risk for the patients' health while performing exercise.

Exclusion criteria

Exclusion criteria were unstable cardiovascular disease, uncontrolled hypertension, severe orthopaedic or neurological disorders making participation in self-administered exercise physically impossible, severe electrolyte imbalances, severe anaemia, expected start of KRT within one year after study recruitment, inability to communicate in Swedish or English, and inability to understand oral instructions.

Power calculation

To detect a difference of at least 60% of the standard deviation at a 5% significance level we calculated to include 50 patients in each treatment group. Allowing for a 30% dropout rate, we aimed to include at least 75 patients in each exercise group.

Randomisation

Randomisation was performed by the statistician (PH), using ProPlac Plan in SAS (SAS Institute, Cary, NC, USA). The block permutations and the size of each block were concealed from all study personnel, apart from the statistician who had no contact with the patients. The randomisation process was designed so that it was not possible to predict which treatment would be assigned to a specific patient. The statistician (PH) generated the random allocation sequence, the nephrologist (MH) enrolled patients, and the research physiotherapist (PS) assigned the exercise intervention to the patients. Due to the nature of the intervention, the research physiotherapist and randomised patients were aware of their exercise treatment group. Remaining recruitment staff were blinded.

Comorbidity evaluation

Assessment of comorbidities with the Davies' Comorbidity Score (125) were performed prior to study inclusion by the nephrologist (MH).

Exercise prescription

The research physiotherapist prescribed the individualised exercise programmes based on each patient's randomisation, baseline physical performance, preferences and exercise goals. Goals were set using the SMART criteria. Exercise was performed self-administered in the patient's home or at a nearby gym. For home-based exercise, the research physiotherapist provided instructions for the exercise programme at the outpatient clinic at Skåne University Hospital. The patients were given dumbbells and weight cuffs to use at home. If the patient chose to perform exercise at a gym, the research physiotherapist gave instructions on how to perform the exercise programme on location, using the existing gym equipment. All exercise sessions were preceded by a warm-up. Exercise sessions were finished with a cool-down period.

Aerobic endurance exercise

All included patients were prescribed aerobic endurance exercise. The standard exercise frequency was set to two days per week but was adapted according to each patient's ability and preference. The exercise intensity for the aerobic endurance exercise was prescribed at a RPE of 13-15 "somewhat hard to hard" on the Borg RPE scale, corresponding to a moderate to vigorous exercise intensity. Exercise duration was prescribed individually according to each patient's capabilities, with the goal of reaching 60 minutes (30 minutes x 2) per week. Examples of activities were walking, running, swimming, cycling, cross-trainer and rowing.

Balance exercise

For the patients randomised to perform balance exercise, the standard exercise frequency was set to three days per week but was adapted according to each patient's ability and preference. The exercise intensity for the balance exercise was prescribed at a RPE of 13-17 "somewhat hard to very hard" on the Borg RPE scale, corresponding to a moderate to vigorous exercise intensity. We used the verbal anchors of the Borg RPE scale to describe "levels of challenge" rather than levels of exertion.

Exercise duration was prescribed individually, with the goal of reaching 90 minutes (30 minutes x 3) per week. Balance exercise was performed as both static and dynamic exercises, with 4-6 exercises in total. For static exercises, holding a position for 30-60 seconds was equal to one repetition, which was repeated for 3-5 sets. Dynamic exercises were performed as 10 repetitions with 2-3 sets.

Examples of static balance exercises used were maintaining balance while standing on one leg, standing with the feet together, standing in a tandem stance, standing on a balance board (single or double stance), planking, or maintaining balance in different positions using a Pilates ball.

Examples of dynamic exercises were walking heel-to-toe, arm reaches while in a double- or single-leg stance, side-shuffles with turns, lunges with rotation, or single-leg deadlifts.

Figure 2. Balance exercises of increasing dificulty
Upper left to right: Tandem stance, Single leg stance, Single leg stance on unstable surface,
Lower left to right: Single leg stance on balance board, Airplane pose on balance board

Resistance exercise

For the patients randomised to perform resistance exercise, the standard exercise frequency was set to three days per week but was adapted according to each patient's ability and preference. The exercise intensity for the resistance exercise was prescribed at a RPE of 13-17 "somewhat hard to very hard" on the Borg RPE scale, corresponding to a moderate to high exercise intensity. Exercise duration was prescribed individually, with the goal of reaching 90 minutes (30 minutes x 3) per week. Resistance exercise was performed with 4-6 exercises in total, for 10 repetitions and 2-3 sets.

Resistance exercises were performed as dynamic exercises for the trunk and the upper and lower extremities, and aimed to include a combination of larger and smaller muscle groups. Examples of resistance exercise used were quadriceps extensions, hamstring curls, squats, step-ups, sit-ups, push-ups, back extensions, biceps curls, overhead press, lat-pulldowns, chest press, or dumbbell rows.

Figure 3. Resistance exercises
From left to right: Quadriceps extension with weight cuff, Biceps curl with dumbell, Overhead press with dumbells.

Exercise diary

All exercise sessions were reported by the patients in a self-kept exercise diary. Patients noted RPE for each individual exercise as well as the duration of the exercise session in minutes, categorized by exercise type. There was also space for the patient to add comments regarding the exercise programme. The exercise diary was sent to the research physiotherapist at regular intervals and followed up via telephone calls.

Follow up and progression of the exercise programme

Follow up and adaptation of the exercise programme was performed by the research physiotherapist. During the first three months of the study, follow up was performed via telephone calls once per week. During the remaining months of the study, follow up was performed via telephone calls every other week.

Progression of the exercise prescription was accomplished with the aim of maintaining exercise intensity within the set goal of RPE 13-15 for aerobic endurance exercise and RPE 13-17 for balance and resistance exercise. Exercise intensity was increased corresponding to the patient's progression and tolerance or reduced in the case of patient deterioration.

Progression of the aerobic endurance exercise could be introduced by increasing the duration of exercise to the goal of 60 minutes per week, by increasing exercise intensity through a higher pace or through increasing load on an exercise bike, cross-trainer or rowing machine. Progression could also be introduced by transitioning to another modality of aerobic endurance exercise, such as from walking to running.

Progression of the balance exercise could be introduced through adapting the exercise intensity, by increasing the time for holding a static position, by using an unstable surface, by performing an exercise with eyes closed, by integrating upper-body movement while maintaining balance in an otherwise static position, by adding light weights, by gradually increasing the pace of the dynamic exercises, or by replacing the exercise with another of greater difficulty.

Progression of the resistance exercise could be introduced through increasing load by changing body position, by increasing the weights, or by replacing one exercise with another of greater difficulty.

Evaluation of physical performance

The assessment of physical performance in the RENEXC-trial was based on the standardized test battery developed and used by the physiotherapists at the Kidney Department of Skåne University Hospital in Lund, with the addition of three supplementary tests to further evaluate walking capacity, muscular endurance and balance. As the RENEXC-trial aimed to be feasible in clinical practice, tests of physical performance were chosen that could be implemented in a clinical setting.

Physical performance was evaluated by the research physiotherapist at baseline and after 4, 8 and 12 months of exercise. An overview of measures of physical performance can be seen in table 4.

Two research physiotherapists were involved in the RENEXC-trial, p1 between October 2011-January 2013 (54 measurements at baseline and 11 measurements at 12 months) and p2 between January 2013-May 2017 (all remaining measurements).

6-minute walk test

Aerobic endurance was evaluated with the 6MWT, a submaximal test, commonly used in patients with CKD (39). This functional test measures the distance a patient can walk indoors on a flat surface for a period of six minutes (126). The patients are instructed to walk as many meters as possible at a self-chosen pace, and standardized encouragement is given according to protocol. Walking aids are allowed (126).

We used reference equations to calculate predicted walking distance for healthy individuals, taking age, sex, weight and height into account (127).

The 6MWT is inexpensive and easy to administer (126). Measurement error has been reported to be 28-29.5 meters in patients on HD (39) and the minimal detectable change (MDC) has been found to be between 60.5-77 meters for patients on HD (128-131). However, a systematic review has shown that a change of 14.0-30.5 m may be clinically important across multiple patient groups such as chronic obstructive pulmonary disease, coronary artery disease, and adults with fear of falling (132). The 6MWT has high reliability in patients with CKD (129, 130), and several studies have examined its validity, however, the summarized quality of evidence is low for validity in patients with CKD (39).

The 6MWT can estimate VO_2peak (133), and studies have shown an association between walking distance in the 6MWT and VO_2peak (134, 135).

Figure 4. The 6MWT

Stair climbing capacity

Aerobic endurance was also evaluated with a stair climbing test, measuring how many flights of stairs a patient could climb at a self-determined pace without stopping. The patient walked up and down ten steps that were 16 cm high and 32.5 cm deep. Twenty steps counted as one flight of stairs. No oral encouragement was given.

Stair climbing tests have been extensively studied and used to evaluate post-operative complications and mortality in thoracic surgery. They can be designed as a maximal test measuring the number of stairs the patient can climb until limited by symptoms, or as a submaximal test with the patient climbing a predetermined number of stairs (136). Stair climbing is regularly used in the clinical setting to evaluate physical function. However, it is not frequently used in research in patients with CKD. To our knowledge, the psychometric properties for stair climbing have not been established in patients with CKD.

Figure 5. Stair climbing capacity

Berg Balance Scale

Balance was evaluated with the Berg Balance Scale (BBS) (137). BBS was developed to evaluate functional balance in elderly patients, including 14 tasks using static or dynamic balance. Tasks evaluated are: moving from sitting to standing, standing unsupported, sitting unsupported, moving from standing to sitting, transfers between chairs, standing with eyes closed, standing with feet together, reaching forward with an outstretched arm, retrieving an object from the floor, turning to look behind, turning 360 degrees, alternately placing a foot on a stool, standing with one foot in front of the other, standing on one foot.

The tasks are rated between 0-4, where 0 indicates the lowest level of function (the patient is unable to perform the task) and 4 indicates the highest level of function (the patient can complete the task fulfilling the specified criteria assigned to it). The score for each task is summarised, with a total score of 56 points. BBS is used frequently in both research and clinical settings in different areas of rehabilitation. It is a valid tool to measure balance in older adults (137) and has high reliability in different clinical populations (138), with MDC between 2.8-6.6 points (139).

Figure 6. Example of items included in Berg Balance Scale
From left to right: Standing with one foot in front of the other, Turning to look back, Stepping onto a step with alternating feet

Functional reach

Balance was also evaluated with the Functional Reach (FR), a dynamic balance test (140). It measures the difference between an arm's length and a maximal forward reach, using a fixed base of support. The test is performed in a standing position. The arm closest to the wall is elevated to a 90-degree flexion of the shoulder with the hand balled into a fist and a yardstick at acromion level. The patient reaches forward as far as possible with the arm adjacent to the wall, without moving the feet or lifting the heels from the floor. The number of cm the 3rd metacarpal has moved from starting point to maximal outreach is measured in centimeters. Three trials are performed of which the average is recorded (140, 141). The FR test has good reliability and validity in older adults (141). To our knowledge, the psychometric properties for FR have not been established in patients with CKD.

Figure 7. Functional Reach

Hand grip strength

Muscular strength in the upper limbs was measured with hand grip strength (HGS), evaluated with the Jamar hand dynamometer (142). The test is performed in a seated position, with the elbow in a 90-degree angle and wrist in neutral position. Three consecutive trials were performed for each hand, with the mean values of the three trials recorded (143).

HGS has high reliability in older adults (144) and in patients with CKD (129, 130). The standard error of measurement (SEM) is between 1.5-2.3kg in patients with CKD (39).

HGS is often used to assess risk of sarcopenia and frailty in older populations and in patients with CKD (144-146).

Figure 8. Hand grip strength

Isometric quadriceps strength

Muscular strength in the lower limbs was evaluated with isometric quadriceps strength (IQS). IQS was measured with a Salter scale connected to a padded wrist cuff by extending the knee against resistance while in a seated position (70). Three consecutive measurements were performed on each leg, and the mean values for each leg were calculated. Measurements were given in kg x cm.

Measuring lower extremity muscle strength and function are useful for assessing a person's ability to perform activities of daily living. Measuring IQS with a Salter scale has been used extensively in the Kidney Department at Skåne University Hospital in Lund. However, there are to our knowledge, no studies evaluating its psychometric properties in patients with CKD.

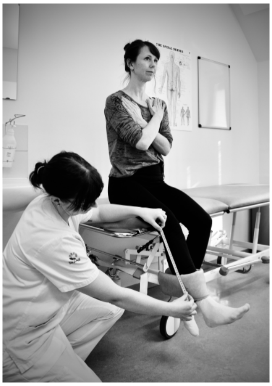

Figure 9. Isometric quadriceps strength

30 second sit-to-stand

Muscular endurance in the lower limbs was evaluated with the STS30 (147). The patient is instructed to stand up fully and sit down as many times as possible during 30 seconds.

There are several versions of the STS tests that are used in patients with CKD. By evaluating the number of STS that a patient can perform within a predetermined time (60 seconds, or 30 seconds) muscular endurance and fatigability is evaluated. Another version evaluates the time it takes to perform a predetermined number of STS, as in the 5-times STS and 10-times STS. These tests reflect explosivity and muscular strength. The STS30 correlates with exercise capacity and is a valid method to evaluate functional capacity in patients on maintenance dialysis (148).

Furthermore, the STS 30 has a high reliability in patients with CKD (148). The SEM is 0.47-0.91 repetitions (128, 148), and the MDC is 2.1-2.6 repetitions in patients on maintenance dialysis (128, 148).

Figure 10. 30 second sit-to-stand

Heel rises and toe lifts

Muscular endurance, muscular strength and function of the lower limbs was evaluated with heel rises and toe lifts.

For heel rises, the patients stood with their back against the wall. Standing on one leg, the patient performed as many heel rises as possible while maintaining height and pace (70). The normative value was 25 heel rises per foot (149).

Figure 11. Heel rises

For toe lifts, the patients stood with their back against the wall and their feet one foot´s length away from the wall. Standing on one leg, the patient performed as many toe lifts as possible while maintaining the height and pace. A pen was passed under the patient's metatarsophalangeal joints to ensure the foot's height during the toe lift (70). The normative value was 20 toe lifts per foot (150).

Figure 12. Toe lifts

Muscular endurance, muscular strength and function in the distal leg muscles is important for mobility. In patients with CKD, muscular fatigue, prevalence of diabetes, peripheral vascular disease and peripheral neuropathy can affect the function of the distal leg muscles. There are to our knowledge, no studies evaluating the psychometric properties of heel rises and toe lifts in patients with CKD.

Moberg pick-up test

The Moberg pick-up test is used to evaluate hand dexterity and was developed by Erik Moberg to follow a patient's status during a rehabilitation process (151). The patient is asked to pick up a set of small, standardized objects (e.g., coins, paper clips, screws) one by one, from a flat surface and place them into a container as quickly as possible. The test is performed with open eyes, and then again with closed eyes (54). However, there are, to our knowledge, no studies evaluating its psychometric properties in patients with CKD.

Figure 13. Moberg pick up test

Table 4. Overview of Outcome Measures of Physical Performance in the RENEXC-trial

	Outcome Measure	Equipement	Method	Ceiling effect	Reference values	Paper
Aerobic endurance	6-minute walk test	30m marked corridor Two cones Stopwatch Measuring wheel Borg RPE scale Optional: Pulse oximeter	To walk as far as possible in 6 minutes. Walking aid allowed. Resting is allowed but timer is not stopped. Standardized oral instructions are given during the test.	yes	Individualised according to sex, age, height and weight (127)	1, 3
	Stair climbing capacity*	Stairs	To walk as many flights of stairs as possible, at a self-determined pace without stopping. No oral encouragement is given.	no	no	1
Balance	Berg Balance Scale	Chair with armrests (average height) Chair without armrests (average height) Yardstick or ruler Step or stool (average height) Slipper or shoe Stopwatch	To maintaine balance during 14 tasks, rated on a scale of 0-4 points. A higher score indicates better balance. Maximum score is 56 points.	yes	Cut-off scores (137)	1, 4
	Functional Reach*	Yardstick	The participant stands next to, but not touching the wall. The arm closest to the wall is elevated to a 90 degree shoulder flexion with the hand balled into a fist, and the patient reaches forward as far as possible with the arm adjacent to the wall, the feet not moving. The number of cm the 3rd metacarpal has moved from starting point to maximal outreach is measured in centimeters.Three trials of which the average are recorded.	yes	Individualised according to age and sex (147)	1, 4
Muscular strength	Hand grip strength*	Jamar hand dynamometer Chair	Sitting postition with the elbow at a 90 degree angle, neutral wrist position. Three trials of which the average is recorded.	no	Individualised according to age and sex (152)	1

	Isometric quadriceps strength*	Salter scale with padded cuff Measuring tape Height-adjustable examination table	Extending the knee against resistance in a sitting postition. Mean value from three consecutive measurements in each leg. Measured in kg x cm (from knee joint to cuff)	no		1, 4
Muscular endurance	30 second sit-to-stand	Chair (average height)	The participant is asked to place their feet at about a shoulder breadth's distance on the floor, one foot slightly in front of the other, wrists crossed, arms folded against chest. Then to stand up and sit down as many times as possible during 30 s. The participant should perform some trial sit-to-stands before testing.	yes	Individualised according to age and sex (153)	1, 4
	Heel rises*	Wall	Starting postition with the back against the wall. On one leg, the patient performs as many heel rises as possible with the same height and tempo.	no	Normative values (n=25) (149)	1
	Toe lifts*	Wall Pen	Starting postition with the back against the wall, feet are placed one foot length out from the wall. On one leg, the patient performs as many toe lifts as possible at a consistent tempo while the foot's height is controlled by passing a pen underneath the forefoot for each lift.	no	Normative values (n=20) (150)	1
Fine motor skills	Moberg pick up test*	Table Chair Desk-blotter Plastic box 10 Small metallic objects Stopwatch	Starting position sitting at a table. 10 objects are placed within a A4 sized rectangle on the desk-blotter. The patient places each item in the plastic box next to the A4 rectangle as fast as possible. The test is performed one hand at a time, and performed with open eyes and with closed eyes, respectivly.	yes	Individualised according to age and sex (54)	1

Note: *Included in the test-battery for patients with CKD, compiled by the physiotherapists at the Kidney Department, Skåne University Hospital, Lund, Sweden. Reference values indicate those used in the RENEXC-trial.

Measures of kidney function

Estimated GFR

Estimation of GFR (eGFR) was performed at baseline and after 4, 8 and 12 months of exercise at the Department of Clinical Chemistry, Laboratory Medicine, Skåne. An estimation of GFR can be calculated by using equations based on endogenous substances such as creatinine and cystatin C. For the RENEXC-trial, eGFR was calculated from a cystatin C and P-creatinine based equation (154).

Measured GFR

Kidney function, measured by iohexol clearance (155), was performed at baseline and after 12 months of exercise. Iohexol is a non-ionic contrast agent with low extra-renal excretion, and as it is neither secreted nor reabsorbed by the kidney it is a suitable marker for GFR. It is given as an intravenous injection and GFR is determined by measuring plasma concentration and elimination rate. In Skåne University Hospital, measurement of iohexol clearance is performed as routine for patients with CKD, with analyses performed at the Department of Clinical Chemistry at Laboratory Medicine, Skåne.

Laboratory analyses

Routine laboratory analyses were performed at baseline and after 4, 8 and 12 months of exercise. The samples were analysed according to accredited methods at the department of Clinical Chemistry, Laboratory Medicine, Skåne.

Evaluation of health-related quality of life

Assessment of HRQOL with the KDQOL-SF (119) was performed at baseline, and after 4, 8 and 12 months of exercise. The KDQOL-SF is a disease specific questionnaire, consisting of 80 items. It is based on eight generic dimensions from the SF-36: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The eight dimensions are aggregated into two summary scores: the Physical Component Summary and the Mental Component Summary (156). Additionally, KDQOL-SF includes a single item evaluating self-perceived change in health status over time. Responses are rated using a Likert scale, and raw scores are linearly transformed to a 0–100 scale, with higher scores indicating better HRQOL (119). KDQOL-SF is validated in patients on dialysis (157) as well as in patients that have undergone KT (158).

Adherence, performance and safety

Adherence

Adherence to the exercise programme and exercise performance was calculated from the self-kept exercise diaries.

Exercise intensity

Exercise intensity for the different types of exercise was calculated as the mean RPE per week.

Exercise duration

Exercise duration for different types of exercise was calculated as mean minutes of exercise per week.

Exercise volume

Additionally, the cumulative amount of exercise, in minutes per week, was calculated.

Safety

The self-administered exercise prescription was based on each patient's physical performance at baseline, taking comorbidities and previous exercise experience into account to ensure that the exercises would be safe to perform self-administered. In case of any exercise-related incidents the patients were encouraged to contact the research physiotherapist. Any harms were assessed clinically.

Statistical methods

Descriptive statistics were presented with means and standard deviations or median and interquartile range or range. Categorical variables were presented as percentage or frequencies. p-values <0.05 were considered significant.

Data were analysed using the R software (R Foundation for Statistical Computing, Vienna, Austria).

Paper 1

Intention to treat analyses was applied, including all randomised patients.

Physical performance and kidney function at baseline and at 12 months were analysed with mixed model analysis using the effects of time, treatment and their interaction as fixed effects and subjects as random effects.

Paper 2

Intention to treat analyses was applied, including all randomised patients. Missing data was handled by using the last observation carried forward method.

KDQOL-results at baseline and at 12 months were analysed with mixed model analysis using the effects of time, treatment and their interaction as fixed effects and subjects as random effects.

Paper 3

Per protocol analyses was applied, including all patients who completed a minimum of two measurements with the 6MWT at 0, 4, 8 or 12 months. Within-group change in walking capacity was analyzed with Student's paired *t*-test. Relationships were analyzed with single and multiple linear regression analyses. Relationships for non-parametric data were analyzed with Spearman's correlation coefficient.

Paper 4

Per protocol analyses was applied, including all patients who performed baseline and 12-month measurements of BBS, FR, STS30 or IQS. Within group change in balance, muscular strength, and muscular endurance were analyzed with Student's paired *t*-test for parametric data or with the Wilcoxon signed-rank test for non-parametric data. Between-group differences were analyzed with the independent samples Student's *t*-test. Relationships were analyzed with single and multiple linear regression analyses. Benjamini–Hochberg false discovery rate procedure was applied across all multiple regression models to account for multiple testing. Both raw and adjusted *p*-values are reported.

Ethical considerations

The RENEXC-trial was approved by the Regional Ethical Review Board in Lund (2011/369) and adhered to the Helsinki declaration. All patients received oral and written information and gave written informed consent. The RENEXC-trial is registered at www.ClinicalTrials.gov: NCT02041156 (retrospectively registered on 17th of January 2014).

Results

Patients

Papers 1 and 2

A total of 217 patients were screened, and 151 patients (53 women, 98 men) were included in the RENEXC-trial. The mean age of the patients was 66 ± 14 years (range 19-87 years), and the mean mGFR was 22 ± 8mL/min/1.73m^2. Baseline characteristics are shown in table 5.

The underlying causes of kidney disease were hypertension (41%), diabetes mellitus (16%), interstitial nephritis (15%), glomerulonephritis (15%), polycystic kidney disease (6%), and others (7%).

Fourteen patients were in CKD stage 3, 93 were in CKD stage 4, and 41 patients were in CKD stage 5.

Table 5. Overview of baseline characteristics of 151 patients (Papers 1 and 2)

	Balance group	Resistance group
Characteristics	Mean (SD)	Mean (SD)
Age (years)	65 (14)	67 (14)
Sex (female/male)	28/47	25/51
Weight (kg)	79 (16)	84 (19)
Height (m)	1.71 (0.1)	1.72 (0.09)
BMI (kg/m^2)	27 (5)	28 (6)
eGFR (mL/min/1.73m^2)	20 (7)	19 (8)
mGFR (mL/min/1.73m^2)	22 (8)	23 (9)
Comorbidities	%	%
Malignancy	12	16
Diabetes Mellitus	27	38
Left Ventricular Dysfunction	13	8
Ischaemic Heart Disease	17	22
Peripheral Vascular Disease	17	24
Systemic collagen vascular disease	9	12
Other significant pathology (e.g. hypertension)	76	76
Note: SD; standard deviation, BMI; Body Mass Index, eGFR; estimated Glomerular Filtration Rate; mGFR; measured Glomerular Filtration Rate		

Three patients randomised to the resistance group discontinued the study before baseline assessments, due to reoccurring retinal haemorrhage, bone fracture and terminal illness. During the 12-month intervention period, 16 patients in the balance group and 20 patients in the resistance group discontinued the study. Reasons for discontinuing were moving to another town, travel, concomitant illness or lacking motivation to continue. Two patients in the balance group and one patient in the resistance group died, for reasons unrelated to the study. The flow of patients through the RENEXC-trial can be seen in figure 14.

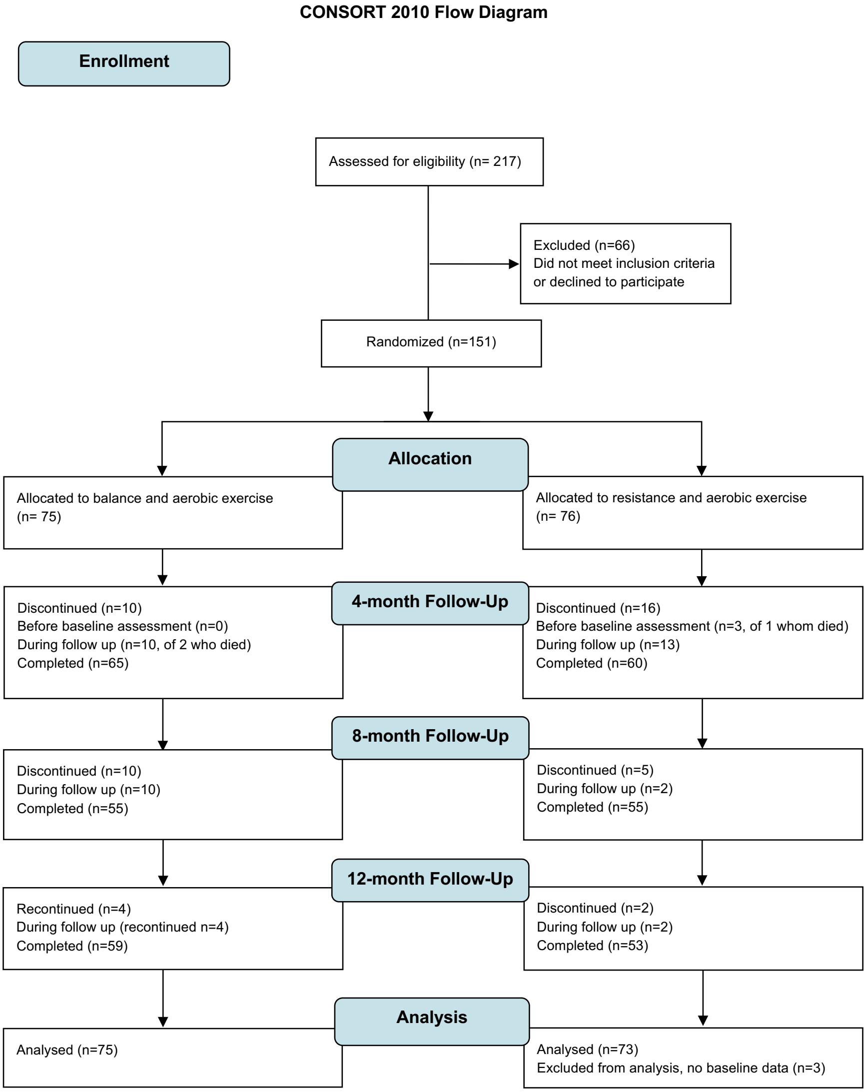

Figure 14. CONSORT Flow chart for the RENEXC-trial

Paper 3

Paper 3 included a subgroup of the RENEXC-trial who performed the 6MWT at baseline. A total of 147 patients (mean age: 66 ± 14 years) performed the 6MWT at baseline. The mean mGFR for these patients was 22 ± 8mL/min/1.73 m2. The 6MWT was performed by 100 patients at the 12-month control.

Paper 4

Paper 4 included a subgroup of the RENEXC-trial, with a total of 148 patients who performed measures of balance (BBS, FR), muscular strength (IQS), and muscular endurance (STS30) at baseline (75 in the balance group and 73 in the resistance group). The patients randomised to the balance group had a mean age of 65 ±14 years and a mean mGFR of 22 ± 8 mL/min/1.73 m2. Patients randomised to the resistance group had a mean age of 67 ± 14 years and a mean mGFR of 23 ± 9 mL/min/1.73 m2.

A total of 112 patients completed the measures of balance, muscular strength and muscular endurance at the 12-month control (59 patients in the balance group and 53 in the resistance group).

Paper 1. Physical performance

Paper 1 compared the effects of 12 months of self-administered balance or resistance exercise, combined with aerobic endurance exercise, on physical performance. The intention to treat analysis showed that all aspects of physical performance were significantly improved in both exercise groups after 12 months of exercise.

Aerobic endurance measured with the 6MWT and stair climbing increased significantly after 12 months of exercise in both groups.

Balance measured with FR improved significantly after 12 months of exercise in both exercise groups. BBS was unchanged.

Muscular strength measured with IQS increased significantly after 12 months of exercise in both exercise groups. HGS was unchanged.

Muscular endurance measured with the STS30 test increased significantly after 12 months of exercise in both exercise groups. Heel rises and toe lifts increased significantly after 12 months of exercise in both groups.

Fine motor skills measured with Moberg pick up test improved significantly in the left hand, when performed with open eyes and in the right hand, when performed with closed eyes after 12 months of exercise in the balance group. Results for both hands were significantly improved with open eyes and closed eyes, after 12 months of exercise in the resistance group.

Difference between groups

There were no significant interaction effects between the exercise groups for estimated effects for any of the physical performance measures after 12 months of exercise. However, significant improvement could be seen earlier in the resistance group compared with the balance group for 6MWT, FR, STS30, toe lifts and the Moberg pick up test.

Effects on physical performance after 12 months of exercise and between-group comparison can be seen in table 6.

Table 6. Physical performance after 12 months of balance or resistance exercise, combined with aerobic endurance exercise

Outcome Measure			Balance group (12 months - baseline)		Resistance group (12 months - baseline)		Between-group comparison (resistance - balance)	
			Est. effects (95% CI)	P-value	Est. effects (95% CI)	P-value	Est. effects (95% CI)	p-value
Aerobic endurance	6-minute walk test (m)		24 (10, 37)	**<0.001**	31 (16, 46)	**<0.001**	7 (13, 27)	0.5
	Stair climbing capacity (n)		5 (3, 7)	**<0.001**	6 (3, 8)	**<0.001**	1 (-2, 4)	0.6
Balance	Berg Balance Scale (points)		0 (-1, 1)	0.9	0 (-1, 1)	0.8	0 (-1, 1)	0.9
	Functional Reach (cm)		2 (0, 3)	**0.008**	2 (1,4)	**0.003**	0 (-2, 2)	0.7
Muscular strength	Hand grip strength (kg)	Right Left	0 (0, 1) 0 (-1, 1)	0.3 0.7	0 (-1, 1) 1 (0, 2)	0.5 0.3	0 (-1, 1) 0 (-2, 2)	0.9 0.6
	Isometric quadriceps strength (kg x m)	Right Left	0.6 (0.1, 1.1) 0.9 (0.3, 1.4)	**0.01** **0.001**	1.2 (0.7, 1.7) 0.8 (0.3, 1.4)	**<0.001** **0.003**	0.1 (0, 0.1) 0 (-0.1, 0.1)	0.1 0.9
Muscular endurance	30 second sit-to-stand (n)		1 (0, 2)	**0.001**	1 (1, 2)	**<0.001**	0 (-1, 1)	0.5
	Heel rises (n)	Right Left	8 (5, 10) 6 (4, 9)	**<0.001** **<0.001**	7 (4, 9) 6 (4, 8)	**<0.001** **<0.001**	-1 (-4, 2) 0 (-4, 3)	0.5 0.8
	Toe lifts (n)	Right Left	6 (3, 8) 4 (3, 6)	**<0.001** **<0.001**	4 (2, 6) 3 (1, 5)	**0.001** **0.003**	-2 (-5, 2) -2 (-4, 1)	0.3 0.3
Fine motor skills	Moberg pick up test Open eyes (s)	Right Left	-0.3 (0.6, 0.0) -0.3 (0.6, 0.0)	0.06 **0.05**	-0.7 (-1.0, -0.3) -0.4 (-0.7, -0.1)	**<0.001** **0.01**	-0.4 (-0.8, 0.1) -0.1 (-0.5, 0.3)	0.1 0.7
	Moberg pick up test Closed eyes (s)	Right Left	-2.4 (-4.7, -0.2) -1.3 (-2.8, 0.3)	**0.04** 0.1	-4.0 (-6.4, -1.7) -1.6 (-3.3, -0.0)	**<0.001** **0.05**	-1.6 (-4.8, 1.7) -0.4 (-2.6, 1.9)	0.3 0.8

Note: Est. effects; Estimated effects by mixed model analysis, 95% CI; 95% confidence intervals

Paper 2. Health-related quality of life

Paper 2 compared the effects of 12 months self-administered balance or resistance exercise, combined with aerobic exercise, on HRQOL.

Most items in KDQOL-SF were unchanged after 12 months of exercise, as shown in figure 15. Specifically, the mental component summary (MCS) and physical component summary (PCS) were unchanged in both groups after 12 months of exercise.

Balance group

According to the linear mixed model analysis, General Health significantly declined over 12 months of exercise (B = -0.31, 95% CI: -0.58 to -0.03).

Resistance group

According to the linear mixed model analysis, Cognitive Function (B = 0.28, 95% CI: 0.07 to 0.48) and General Health (B = 0.32, 95% CI: 0.10 to 0.54) significantly improved over 12 months of exercise.

Sexual Function significantly declined (B = -0.42, 95% CI: -0.76 to -0.07) over 12 months of exercise.

Group comparison

There was a significant interaction effect between time and treatment for Cognitive Function (B = 0.43, 95 % CI: 0.10 to 0.76), General Health (B = 0.62, 95% CI: 0.27 to 0.97), and Patient Satisfaction (B = 0.38, 95% CI: 0.04 to 0.71) showing a significantly more favourable trajectory over time in the resistance group compared with the balance group (figure 15).

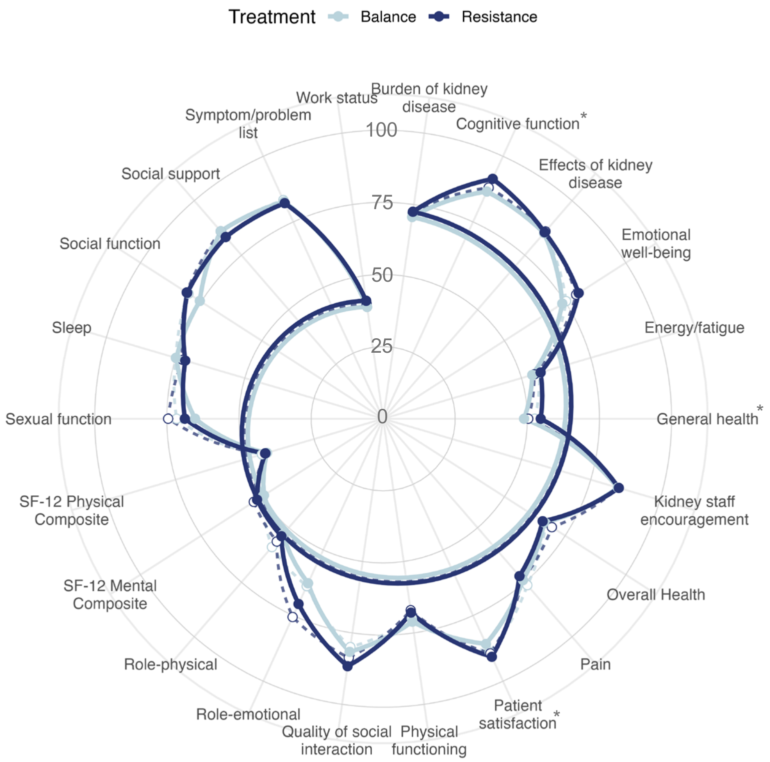

Figure 15. Mean scores for KDQOL at baseline and after 12 months of exercise
Month 0 = dashed line, Month 12 = solid line. The distance from the centre reflects the domain score (0–100), where values closer to the outer ring indicate better HRQOL. * indicates a significant interaction effect in favour of the resistance group. Work status is connected to burden of kidney disease by the inner circle.

Papers 3 and 4. Adherence, performance and safety of the exercise programmes and relationships between baseline physical performance, exercise performance and change in measures of physical performance

Change in aerobic endurance, balance, muscular strength, and muscular endurance – a per protocol analysis

In papers 3 and 4 a per protocol analysis showed that the 6MWT, FR, IQS, STS30 improved significantly after 12 months of exercise in both exercise groups. Balance measured with BBS was unchanged in both groups. There were no significant between-group differences in mean change of balance and strength measures after

12 months of exercise. An overview of the results for per protocol analysis of aerobic, balance, muscular strength, and muscular endurance are shown in table 7.

Table 7. Results for per protocol analysis of measures of balance, muscular strength, muscular endurance and aerobic endurance at baseline and after 12 months of exercise

Outcome measure										
					Aerobic endurance (all patients)					
					Baseline (n=147)	12 months (n=100)				p-value
6MWT (m)					402 (137)	460 (130)				**<0.001**
		Balance group					**Resistance group**			
	n	Baseline	n	12 months	p-value	n	Baseline	n	12 months	p-value
BBS (points)	73	55 (51-56)	59	56 (53-56)	0.081[1]	72	54 (49-56)	50	56 (53-56)	0.287[1]
FR (cm)	74	34 (9)	57	36 (8)	**0.007**	72	32 (9)	53	36 (7)	**0.003**
IQS right (kgxcm)	73	1139.7 (410.1)	56	1213.8 (427.6)	**0.017**	71	1148.1 (410.1)	49	1332.0 (435.6)	**<0.001**
IQS left (kgxcm)	73	1105.0 (417.5)	56	1192.6 (437.5)	**<0.001**	71	1160.4 (426.4)	50	1305.2 (494.9)	**0.016**
STS30 (n)	74	12 (6)	59	13 (8)	**0.013**	73	11 (6)	50	13 (7)	**<0.001**

Note: 6MWT; 6-minute walk test, BBS; Berg Balance Scale, FR; Functional Reach, IQS; Isometric Quadriceps Strength, STS30; 30 seconds sit-to-stand test. Values are presented as medians (25-75th percentile) for Berg balance scale or means (standard deviation) for remaining measurements. P-values from Wilcoxon signed-rank test[1] or the paired *t*-test less than 0.05 were considered significant.

Adherence, performance and safety

As shown in the CONSORT flow chart (figure 14), 21% of the patients in the balance group and 30% of the patients in the resistance group discontinued the study during the 12-month intervention period. An overview of results for reported RPE and exercise duration is shown in table 8.

Aerobic endurance exercise

As reported in paper 3, 147 patients performed the 6MWT at baseline and 100 patients performed the 6MWT at the 12-month control. Some patients were not able to perform a full 6 minutes of walking during the 6MWT and needed to terminate the test before the 6 minutes had passed. The patients who could not perform 6 minutes of walking had a significantly higher prevalence of diabetes mellitus (p=0.008) compared with patients who completed 6 minutes of walking. Out of the nine patients who terminated the 6MWT prematurely at baseline, seven patients did not perform the 6MWT at the 12-month control. The patients who did not perform the 6MWT at the 12-month control (n=47) had a significantly shorter walking distance ($p < 0.001$) at baseline and a significantly higher prevalence of diabetes mellitus ($p=0.018$) than the completers.

Table 8. RPE and exercise duration - proportion of completers reporting data: median RPE and exercise duration and proportion reaching the prescribed goals.

	Balance exercise	Resistance exercise	Aerobic endurance exercise
Patients at baseline	n= 74	n= 73	n= 147
Completers	n= 59	n= 53	n= 100
Patients reporting RPE (%)	71 %	74 %	80%
RPE (median (25^{th}-75^{th} percentile))	14 (13-15)	14 (13-15)	13 (13-15)
Patients reaching goal RPE (%)	59 %	68 %	74%
Patients reporting exercise duration (%)	86 %	91 %	86%
Duration of exercise, minutes per week (median (range))	38 (3-194)	62 (7-178)	61 (1-840)
Patients reaching goal exercise duration (%)	8 %	21 %	52%
Note: RPE; Rating of Perceived Exertion			

Safety

No harms or exercise related incidents were reported during the continuous follow up via telephone calls, clinical visits or in the exercise diaries in either exercise group.

Relationship between baseline physical performance, exercise performance and change in measures of physical performance

Aerobic endurance exercise

Results from paper 3 showed that patients could perform exercise within the prescribed RPE irrespective of their walking distance at baseline, as there was no significant association between reported RPE of the performed exercise and walking distance at baseline.

There was a positive correlation between the reported exercise duration and baseline walking distance ($p= 0.039$), indicating that patients with a shorter walking distance at baseline performed less minutes of aerobic endurance exercise/week.

No significant relationship was found between improvements in walking distance after 12 months of exercise, and baseline walking distance. Furthermore, no significant relationships were found between improvement in walking distance after 12 months of exercise, and RPE or duration of the aerobic endurance exercise. These results indicate that patients who performed exercise with a longer duration or at a higher intensity per week, did not show a greater improvement in walking distance.

Figure 16 displays the distribution of change (Δ) in 6MWT across different categories of weekly exercise duration. Across all durations, the distributions of Δ walking distance appear relatively similar, with no consistent trend or systematic shift observed.

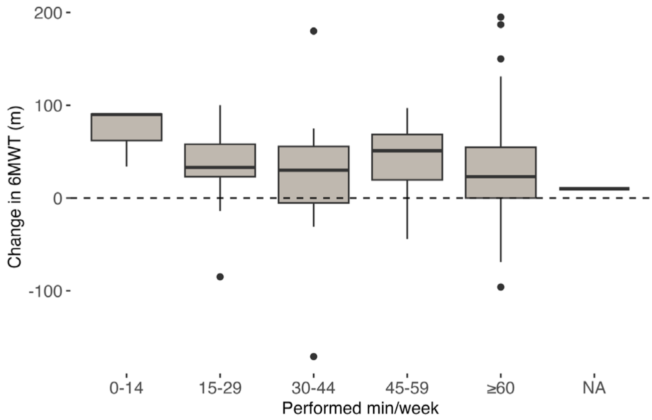

Figure 16. Change in walking distance in the 6MWT (meters) after 12 months for patients grouped according to different levels of exercise duration per week

Balance and Resistance exercise

Results from paper 4 showed that patients could perform exercise within the prescribed RPE, irrespective of baseline results for balance, muscular strength and muscular endurance, as there was no significant association between reported RPE of the performed balance or resistance exercise and results for BBS, FR, IQS and STS30 at baseline.

There were no significant associations between weekly exercise duration and baseline measures in either exercise group.

No significant associations were observed between improvement in balance, muscular strength, and muscular endurance after 12 months of exercise and baseline results in BBS, FR, IQS and STS30.

There were no significant associations between improvement in balance, muscular strength, and muscular endurance after 12 months of exercise and weekly RPE or weekly duration. These results indicate that patients who performed exercise with a higher intensity or longer duration per week did not show a greater improvement in balance, muscular strength or muscular endurance. Figure 17 displays the distribution of change (Δ) in balance and strength measures across different categories of weekly exercise duration for the balance group and resistance group, respectively. Across all durations, the distributions of Δ balance and Δ strength appear relatively similar, with no consistent trend or systematic shift observed.

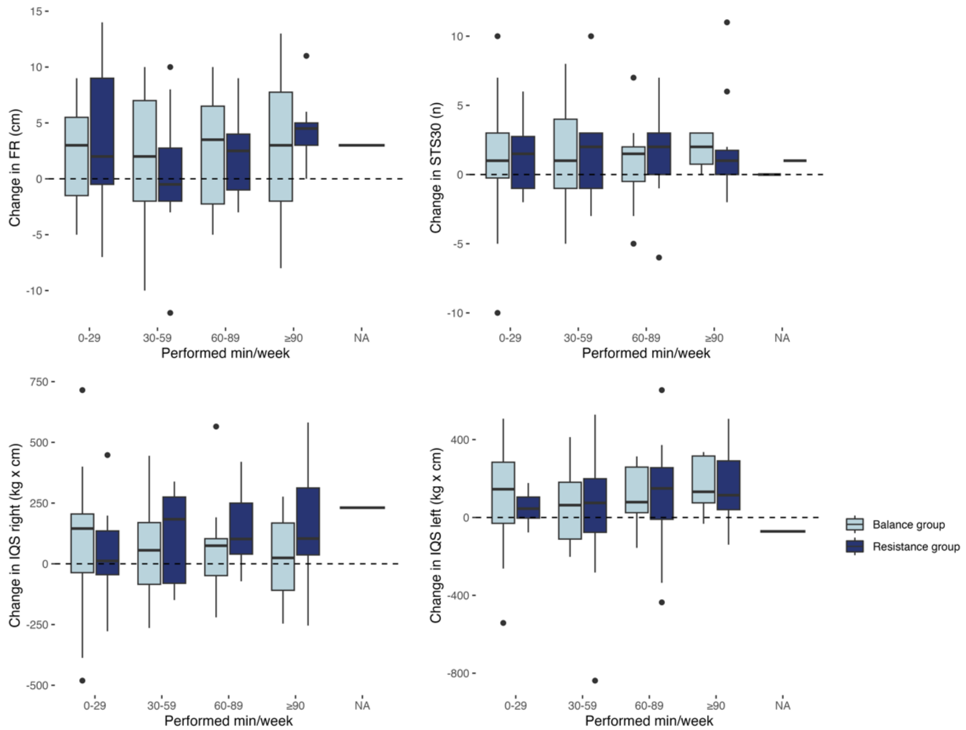

Figure 17. Change in FR, IQS and STS30 after 12 months for patients grouped according to different levels of exercise duration per week

Discussion

The overall aim of this thesis was to investigate the effects of self-administered, individualised, long-term exercise on physical performance and health-related quality of life, and how exercise could safely and efficaciously be prescribed and monitored in patients with CKD 3-5. Results showed that the exercise programmes of the RENEXC-trial were safe and efficacious, improving objective measures of physical performance to the same extent in both exercise groups, as well as maintaining HRQOL, as demonstrated by PROMs, in both exercise groups.

Exercise prescription and monitoring with the Borg scale

Our study is unique in using the Borg RPE scale for prescribing and monitoring exercise intensity for all types of exercise in our exercise intervention. Using the Borg RPE scale to self-monitor exercise intensity can enhance patient empowerment by improving self-awareness, self-efficacy, and enabling patients to take a more active role in managing their exercise progression (44). While the Borg scale has been used to prescribe aerobic endurance and resistance exercise in patients with CKD, no studies have used the Borg scale to prescribe and monitor exercise intensity for balance exercise. As there is no consensus on how to prescribe exercise intensity for balance exercise, and exercise intensity is rarely reported in exercise trials (159), we chose to extend the use of the Borg scale to balance exercise. This enabled communication around exercise intensity and progression of the balance programme, rather than introducing an additional method. However, the Borg scale has not been validated as a method for balance exercise. We used the verbal anchors of the Borg scale to describe levels of challenge rather than levels of exertion when prescribing and monitoring balance exercise. The results of our study showed a high adherence in reporting exercise intensity with the Borg scale for all types of exercise. No exercise-related incidents or harms were reported during the 12-month intervention period indicating that the exercise prescription was safe. As most of the patients in both exercise groups were able to perform exercise within the target RPE as well as significantly improve or maintain physical performance and HRQOL, our findings suggest that the Borg scale can be useful, not only for prescription of self-administered aerobic endurance and resistance exercise, but also for balance exercise in patients with CKD. However, additional research is required to confirm these findings.

Our results in paper 3 showed that the prescribed RPE of 13–15 for aerobic endurance exercise was achievable regardless of the patient's baseline walking distance measured with the 6MWT. There were no significant relationships between baseline measures and RPE. Similarly, paper 4 showed that patients were able to achieve the target RPE of 13-17 for balance and resistance exercise, irrespective of their baseline balance and strength measured with BBS, FR, IQS and STS30. These results indicate that using the Borg RPE scale for prescribing and monitoring exercise intensity is achievable and safe even for deconditioned patients performing self-administered exercise. As many patients with CKD have a high comorbid burden and low levels of physical performance, this is of great importance when prescribing self-administered exercise programmes in patients with CKD.

Our results showed that the Borg RPE scale was an adhered to, safe, and efficient method for prescribing and monitoring self-administered, individualised long-term exercise, resulting in significantly improved or maintained physical performance after 12 months of exercise and maintained or improved HRQOL.

Exercise duration

An important finding of this thesis was that measures of aerobic endurance, balance, muscular strength and muscular endurance significantly improved, irrespective of the performed weekly exercise duration, as shown in papers 3 and 4. This indicates a non-linear dose-response relationship for exercise, in agreement with studies showing that the greatest benefits for health are when an individual goes from being sedentary to performing short durations of weekly exercise, and that substantial health benefits can be achieved even with short durations of exercise (160, 161).

Paper 3 showed a significant association between weekly exercise duration and baseline walking distance measured with the 6MWT. Patients with a short walking distance at baseline performed less minutes of exercise per week. This association is probably enhanced as exercise duration was prescribed according to each patient's tolerance. A shorter walking distance in the 6MWT indicates lower aerobic endurance capacity, meaning that the patient may have difficulty sustaining aerobic endurance exercise over a longer period. There were no associations between exercise duration and the baseline results in BBS, FR, IQS and STS30, as shown in paper 4. However, the balance and resistance exercise were prescribed with a predetermined number of exercises, which most likely explains the non-significant association between exercise duration and baseline results for balance and strength.

There was a wide range of weekly exercise durations for all exercise types. Only half of the included patients could perform aerobic endurance exercise in accordance with the target exercise duration for the RENEXC-trial of 60 minutes/week, as shown in paper 3. Similarly, paper 4 demonstrated that few patients met the target of 90 minutes balance (8%) or resistance (21%) exercise per week. As the current recommendations advise patients to perform 150 minutes of aerobic endurance exercise per week (2), these results highlight a considerable discrepancy between exercise recommendations and clinical reality, and consequently the importance of an individualised exercise programme. Our findings support the use of shorter exercise sessions in patients with CKD, with an exercise duration adapted according to each patient's tolerance. Given the high comorbid burden and low physical performance that is commonly observed in patients with CKD, this approach can minimize fatigue and help patients incorporate exercise into daily life.

In summary, improvements of physical performance were achieved when RPE was kept within the prescribed interval, irrespective of exercise duration, for all types of exercise.

Exercise setting

The RENEXC-trial is one of few exercise trials that have examined self-administered exercise for a longer intervention period in patients with CKD. While in-centre exercise may facilitate a more specific progression rate and enable exercise to be performed at a higher intensity, potentially resulting in larger improvements of physical performance, it is not sustainable to perform in-centre exercise for an unlimited time due to limited resources. Our goal was to promote integration of exercise into the daily life of our patients. We chose to further this goal with self-administered exercise and regular follow up phone calls. Patients could choose to perform the self-administered exercise either at home, outdoors or at a nearby gym, according to preference. Performing exercise self-administered gives the patient more flexibility, both regarding when and where to exercise, as well as being able to adapt exercise duration to an individual's tolerance and capabilities. Self-administered exercise also means little or no travel time, which can be important to patients who live far away from the hospital. Our results demonstrated a safe and efficacious way to prescribe and monitor self-administered exercise, which proved to be feasible in the long-term.

Adherence to self-administered exercise

The overall adherence to the exercise programmes in the RENEXC-trial were high, with 74% of the patients completing the 12-month intervention period, and the number of patients who discontinued the study in line with the anticipated loss to follow up rate. These results are in accordance with a study by Hiraki et al. with a total of 36 patients randomised and a 77% adherence for the 12-month intervention period (91). Conversely, the LANDMARK trial had an adherence rate of 70 % during the initial eight weeks of in-centre exercise, followed by self-administered exercise for 10 months where adherence was assessed by the average weekly amount of physical activity reported by the patients. Physical activity levels increased during the initial six months of the study but then decreased at 12 months (65). In the study by Weiner et al. (66), the initial six months consisted of three in-centre exercise sessions per week, with a 59.5% adherence rate. After the initial six months, the patients transitioned to the maintenance phase of the study where they could choose to perform one of the three weekly sessions self-administered for the remaining six months of the study. The adherence rate for the maintenance phase was somewhat lower (48.9%) than the initial phase of the study (140). Similar results were shown in a study by Mustata et al., who combined in-centre exercise with self-administered exercise during a 12-month intervention period. The in-centre exercise sessions had an adherence rate of 80 %, but the self-administered exercise sessions only had a 20% adherence rate (97).

Key factors for the high adherence during the 12-month intervention period of the RENEXC-trial include highly individualised exercise programmes and regular follow up via phone contact. As the exercise programmes were prescribed with each patient's preference and goals in mind as well as their current level of physical performance, we believe that this increased the meaningfulness for the individual and laid the groundwork for finding an exercise regime that the patient could maintain in the long-term. The research physiotherapist used the SMART criteria to specify goals, to promote behavioural change (62) and provided clear instructions and demonstrations when prescribing exercise (44). The SMART goals were followed up regularly during the follow up, both via phone contact and during the in-centre follow up.

Studies show that encouraging patients to self-monitor their behaviour have higher success rates regarding behavioural change (162). In the RENEXC-trial, patients documented their exercise routine in an exercise diary, affirming their ability to exercise within the prescription. Furthermore, they received personalised positive feedback via the regular follow up phone contacts, contributing to improved self-efficacy (44). The in-centre follow up provided additional motivation and enabled more specific and individualised progression of the exercise programme than what was possible via phone contact.

A review article summarising facilitators and barriers to exercise, highlighted that support from a healthcare professional is an important motivating factor for exercise adherence (69). In the RENEXC-trial, all members of the multidisciplinary team, including physiotherapist, nephrologist, renal failure nurse, and dietician, were involved in emphasizing the importance of exercise during every visit, further supporting the patients in maintaining regular exercise habits. This is consistent with other studies (65, 109) that included regular follow up as a method to sustain self-administered exercise in patients with CKD. By addressing barriers to exercise, such as medical conditions and physiological challenges like fatigue, frailty, and low physical performance (69) and by individualising the exercise programme and progression plan, many obstacles can be overcome, making it feasible even for deconditioned patients to perform exercise.

The drop-out analysis performed in paper 3, showed that patients who discontinued the study had a significantly shorter walking distance at baseline and a higher prevalence of diabetes mellitus than the patients who completed the study. This indicates that patients with poor walking capacity and higher comorbid burden may need additional support to maintain a long-term exercise programme, either through more frequent follow up or through in-centre exercise. By identifying patients who may need more support in sustaining an exercise programme, resources can be allocated more efficiently.

Physical performance

Both the intention to treat analysis (paper 1) and the per protocol analysis (papers 3 and 4) showed that 12 months self-administered exercise resulted in improved or maintained physical performance in both exercise groups.

Aerobic endurance

Aerobic endurance was significantly improved after 12 months of exercise, which is consistent with results from meta-analyses in patients with CKD, not on KRT (67, 82, 83, 87). However, the RENEXC-trial is unique in demonstrating significant improvements after a self-administered exercise intervention during a period of 12 months.

Balance

Balance measured with FR was significantly improved after 12 months of exercise in both exercise groups. These improvements are in agreement with results from meta-analyses that showed improvement in TUG after exercise (67, 82, 83).

However, most of the included studies have focused on aerobic and/or resistance exercise. To our knowledge, only one study (163), not included in the meta-analyses above had incorporated balance exercise as part of the exercise programme for patients with CKD, showing significant improvements in the TUG, the ISWT and 60 second STS (163).

The RENEXC-trial is, to the best of our knowledge, the first study to examine balance exercise combined with aerobic endurance exercise as an exercise intervention, demonstrating that this type of exercise programme can maintain and increase physical performance after 12 months of exercise in patients with CKD. Interestingly, secondary analyses of the RENEXC-trial using dual-energy X-ray absorptiometry (DEXA), showed that the balance group seemed to preserve and enhance bone-mineral density more effectively compared with the resistance group (164) and also achieved significant improvements in muscle mass in the lower extremities and whole-body after 12 months of exercise, while muscle mass in the resistance group was unchanged (165). These sub studies indicate the usefulness of balance exercises for patients with CKD, and more studies examining the effects of balance exercise are needed.

Balance exercise in combination with aerobic endurance exercise resulted in significant improvements, not only in measures of aerobic endurance and balance but also in measures of muscular strength and endurance in the lower extremities after 12 months of exercise as shown in papers 1 and 4. As both exercise groups in the RENEXC-trial performed aerobic exercise it is not possible to isolate the effects of the balance or resistance exercise. This is demonstrated in earlier trials with aerobic exercise interventions that have shown benefits in balance, muscular strength and muscular endurance in patients with CKD (99, 109).

Results in BBS was unchanged after 12 months of exercise in both groups, as reported in papers 1 and 4. The mean baseline scores of the BBS were near the maximum achievable score (54/56 points), indicating a ceiling effect. As a result, no significant improvement was observed in this test. It is important to note that the natural course in CKD is for physical performance to decline with the deterioration of kidney function (18), and that maintaining physical performance over time can be regarded as a positive outcome of an exercise programme, as seen in BBS.

Muscular strength and muscular endurance

There were significant improvements of muscular strength and muscular endurance after 12 months of exercise in both exercise groups. These results are in agreement with results from studies that show improvement in muscular strength and muscular endurance in the lower extremities after exercise interventions (91, 103, 104, 109, 163). Meta-analyses showed significant effects of exercise using different versions of the STS test (67, 82), but few studies have evaluated quadriceps strength as an outcome measure, and to our knowledge, no studies have evaluated heel rises and toe lifts, which measure muscular endurance in the lower leg, as outcome measures of physical performance.

HGS was unchanged, as shown in paper 1. This is consistent with results from the LANDMARK trial (65) and two meta-analyses examining exercise interventions in patients with CKD. Conversely, a significant effect on HGS was found in a meta-analysis examining the effect of resistance exercise in patients with CKD (87). In resistance exercise, HGS can be directly improved by performing exercises involving the hand and or forearm as in the study by Hiraki et al. who included a hand grip strengthening device in their exercise programme (91), or indirectly improved by being engaged while using the upper limbs to perform tasks such as lifting weights or performing exercises with dumbbells or other equipment. No hand grip specific exercise was used in the RENEXC-trial.

Although HGS is used as a marker of frailty (146), nutritional status (145) and mortality (166) in patients with CKD, it does not seem to be a meaningful way to evaluate the effects of exercise programmes on general physical performance.

Statistical significance versus clinical significance

When designing the RENEXC-trial, the outcome measures were based on the existing test-battery used at the Kidney Department of Skåne University Hospital in Lund, with the addition of three outcome measures. However, only two of the improved outcome measures have established values for standard error of measurement and minimal clinical important difference.

6MWT

Patients in the RENEXC-trial improved walking distance in the 6MWT with 24 (95% CI 10-37) meters in the balance group and 31 (95% CI 16-46) meters in the resistance group. The measurement error threshold is 28-29.5 meters in patients on HD (39), meaning that the improvements in the balance group were below the threshold and the results in the resistance group, just managed to exceed the measurement error threshold. In the pooled per protocol analysis in paper 3, walking distance improved with 30 ± 56 meters, just exceeding the threshold for measurement error.

While the increase in walking distance did not meet the MDC of 60.5-77 meters established for patients with HD (128-131), the minimal clinically important difference (MCID) for several other patient populations have been reported to be lower (14-30.5 meters) (132). Furthermore, a secondary analysis of the EXCITE trial showed a decrease in mortality of 11% for every 20-meter increase in walking distance (167). In the RENEXC-trial a survival analysis showed that patients who improved their 6MWT by 5% or more had a better survival compared with patients who did not complete the study (168). Considering these results and that smaller changes in walking distance have been identified as clinically meaningful in other patient populations, the improvement in 6MWT in the RENEXC-trial most likely has clinical meaningfulness.

STS30

The improvements in STS30 were 1 (95% CI 0-2) repetitions in the balance group and 1 (95% CI 1-2) repetitions in the resistance group, just exceeding the threshold for measurement error 0.71-0.91 repetitions (39). Although STS30 was significantly improved in both exercise groups, the improvement did not exceed the established MDC of 2.1-2.6 repetitions (128, 148). In analogy with the survival benefits shown for improvement in 6MWT in the RENEXC-trial, an improvement in STS30 was associated with better survival compared with non-completers (168). Thus, considering the expected disease-related decline of muscular strength and muscular endurance patients with CKD, maintaining or slightly improving physical function can be argued to be of clinical relevance.

Health-related quality of life

In paper 2, results showed that resistance exercise combined with aerobic exercise may be more efficient in improving HRQOL over time compared with balance exercise combined with aerobic endurance exercise. However, most subscales in the KDQOL were maintained after 12 months of exercise in both exercise groups, suggesting that both balance and resistance exercise, combined with aerobic endurance exercise, can contribute to maintaining HRQOL in patients with CKD 3-5.

Statistical significance versus clinical significance

The MCID in KDQOL is yet to be established. While a change of 3-5 points in RAND-36 scores have been shown to be clinically important in different populations, it can be argued that smaller changes in HRQOL can be of clinical significance (169).

The subscale for Cognitive function had a significantly favourable trajectory in the resistance group compared with the balance group. The estimated effect was B = 0.43 per month, corresponding to a 5.16-point difference over 12 months, which meets the MCID values for the RAND-36. Interestingly, the EXCITE-trial showed improvements for Cognitive function measured with KDQOL in the exercise group compared with the control group after their 6-month walking intervention (109). These results are in line with a systematic review and meta-analysis showing that aerobic exercise was associated with the greatest improvement in cognitive function compared to other exercise types in healthy individuals, followed by resistance exercise (170). As both groups in the RENEXC-trial performed aerobic endurance exercise, this may have contributed in maintaining HRQOL, while the addition of resistance exercise resulted in a significantly greater improvement over time compared with balance exercise.

The subscales for General health (B = 0.62, corresponding to a 7.44-point difference over 12 months) and Patient satisfaction (B = 0.38 corresponding to a 4.56-point difference over 12 months), also demonstrated significantly favourable trajectories over time that can be considered clinically relevant. This is in agreement with the results from a meta-analysis showing that exercise interventions significantly improve General health in patients with CKD, not on KRT (82).

Both the decline in General Health (B = -0.31, corresponding to a – 3.72-point difference) over 12 months in the balance group and the decline in Sexual function (B = -0.42, corresponding to a – 5.04-point difference) in the resistance group can be considered clinically significant.

Few studies have examined the effects of longer exercise interventions (≥24 weeks) on HRQOL in patients with CKD not on KRT (93, 97, 101, 102). However, sustainability of an exercise programme is important as patients with chronic illness continue to live with their condition beyond the intervention. While more long-term studies are needed to explore the effects of exercise on HRQOL, we have shown that self-administered resistance and balance exercise, combined with aerobic endurance exercise can contribute to maintaining and improving HRQOL in patients with CKD not on KRT.

Group comparisons

Paper 1 showed that many aspects of physical performance were improved earlier in the resistance group compared with the balance group. Paper 1 also showed that urine-albumin-creatinine ratio (U-ACR) was significantly decreased in the resistance group compared with the balance group. Paper 2 showed more favourable trajectories for HRQOL in the resistance group compared with the balance group. However, the long-term effect of exercise on physical performance was equal in both groups. Sub studies of the RENEXC-trial showed beneficial effects on bone density (164), and muscle mass (165) in the balance group compared with the resistance group.

The adherence to the exercise programme was similar in both exercise groups, demonstrating that both types of exercise were sustainable to perform self-administered for 12 months.

In conclusion, both types of exercise achieved important health-benefits for patients with CKD. Most likely, a combination of individually adapted exercise types is the best approach, as multicomponent interventions can address different aspects of physical performance and health. Our study is the first to include balance exercise as a specific intervention in patients with CKD, providing a unique contribution by extending the knowledge regarding exercise in patients with CKD.

Methodological considerations

Limitations

There are some methodological limitations in the studies of this thesis.

Lack of a sedentary control group

Prescription of exercise is part of standard care at our department; therefore, a sedentary control group was deemed unethical when designing the RENEXC-trial. However, while this limits the comparative interpretation of our data, our study is the first head-to-head study comparing the effects of two different types of exercise in patients with CKD, not on KRT.

Blinding

Due to the nature of the intervention, it was not possible to blind the patients to the exercise group to which they had been randomised. Furthermore, the research physiotherapist's dual role in prescribing exercise and assessing the patients' physical performance did not permit blinding, and due to budgetary constraints, it was not feasible to employ two research physiotherapists for the whole intervention period of the RENEXC-trial. However, the research physiotherapist adhered to a standardized protocol, thus minimizing risk of bias.

Psychometric properties of the outcome measures

As the outcome measures for physical performance were based on the existing test-battery used in clinical routine at our department, several of the outcome measures lack psychometric properties for patients with CKD. However, as the study was designed to reflect the routine clinical setting at our department, we chose to use the outcome measures already integrated at the clinic. To strengthen the results, we added three measures of physical performance which were regularly used in clinical research and had data on psychometric properties. Since the RENEXC-trial the 6MWT and STS30 have been implemented into clinical routine at the Kidney Department of Skåne University Hospital.

Another methodological aspect to consider is that repeated assessments may introduce a learning effect for the outcome measures. We aimed to minimize this effect by using standardized instructions and protocols, as well as familiarisation trials according to the different outcome measures' instructions.

Maintaining consistency in assessments of physical performance and exercise prescription

The research physiotherapist was replaced after a year of the RENEXC-trial. To maintain consistency of exercise prescription and data collection, a period of overlap was implemented during which both physiotherapists performed assessments and exercise prescription together. Furthermore, both physiotherapists followed the standardized instructions for the assessments of physical performance and the guidelines for exercise prescription that were established for the RENEXC-trial.

Exercise monitoring

Performed exercise was reported in self-kept exercise diaries and followed up via phone contact. By including objective measures, such as accelerometers or wearable activity trackers, more accurate data on exercise habits could have been acquired. However, when the RENEXC-trial was designed, accelerometers and other objective activity-monitors were not widely available or used in clinical practice.

Follow up in the RENEXC-trial was performed via phone contact, with four in-centre follow ups performed during the 12-month intervention period. With current technological possibilities, a more interactive follow up such as via video calls could have been performed, providing a more specific follow up and monitoring of progression of the exercise programme.

Statistical considerations

In paper 3, within group change over time was analysed with paired t-tests. In retrospect, a repeated measures ANOVA or a mixed model analysis would have been more appropriate to avoid inflation of type 1 error due to multiple testing.

Strengths

The RENEXC-trial has several strengths. It was designed so that the exercise programme and outcome measures would be feasible to implement in a clinical setting. Inclusion criteria were open, enabling the results of the RENEXC-trial to be applicable to a representative CKD population. Moreover, the RENEXC-trial had a large sample size and was performed with a 12-month long exercise intervention, demonstrating the sustainability of the exercise programme. It is, to our knowledge, the largest exercise trial in patients with CKD, not on KRT, providing unique insights into how self-administered exercise can be prescribed and monitored in patients with CKD.

Clinical Implications

The findings in this thesis increase knowledge of the effects of self-administered, individualised, long-term exercise on physical performance and health-related quality of life, and how exercise can be prescribed and monitored in patients with CKD 3-5, not on KRT.

- Both balance and resistance exercise, combined with aerobic endurance exercise, maintained or improved physical performance after a 12-month intervention period.
- Both balance and resistance exercise, combined with aerobic endurance exercise, maintained most aspects of HRQOL after a 12-month intervention period. Resistance exercise combined with aerobic endurance exercise showed more favourable trajectories for HRQOL over time.
- Using the Borg scale, to prescribe and monitor exercise intensity, facilitated communication between patients and the physiotherapist by using the verbal anchors associated with the Borg scale. The verbal anchors were slightly adapted for balance exercise, signifying levels of challenge rather than levels of exertion. This enabled follow up and progression of the self-administered exercise programme via phone contact for all types of exercise.
- Patients were able to perform exercise within the prescribed RPE 13-15 for aerobic endurance exercise and the RPE 13-17 for balance and resistance exercise. Prescription and progression of exercise intensity with the Borg scale was safe and efficacious for self-administered exercise.
- Exercise duration varied widely between patients. Many patients were not able to reach the recommendations for duration for patients with CKD. However, significant improvements of physical performance were achieved irrespective of weekly exercise duration, within the prescribed RPE using the Borg scale. This is important knowledge when prescribing exercise, highlighting the importance of individualised exercise programmes with shorter, more manageable exercise durations to minimize barriers to exercise.
- The exercise programmes, prescribed and monitored with the Borg scale, and regularly followed by the physiotherapist, were sustainable in the long-term.

Conclusions

The overall conclusions of this thesis are that

- 12 months of self-administered, individualised, balance and resistance exercise, both in combination with aerobic endurance exercise, resulted in significantly improved or maintained physical performance and maintained or significantly improved HRQOL.
- The Borg RPE scale was a safe and efficacious method for prescribing and monitoring 12 months of self-administered, individualised exercise in patients with CKD 3-5.
- Regular contact with a physiotherapist most likely facilitated adherence.

Specific conclusions are that

Paper 1.

- 12 months of self-administered, individualised, balance and resistance exercise, both combined with aerobic endurance exercise, significantly improved or maintained physical performance, with no differences between exercise groups.

Paper 2.

- 12 months of resistance exercise in combination with aerobic endurance exercise, resulted in significantly more favourable trajectories for HRQOL regarding Cognitive function, General health and Patient Satisfaction compared with balance exercise in combination with aerobic endurance exercise.
- Both groups maintained most and improved some subscales in the KDQOL-SF indicating that 12 months of self-administered, individualised balance and resistance exercise, combined with aerobic endurance exercise, could contribute to preserving HRQOL in patients with CKD 3-5.

Paper 3.

- The Borg scale was safe and adhered to when prescribing and monitoring 12 months of self-administered aerobic endurance exercise.

- The Borg scale was efficacious when the prescribed RPE was kept between 13 and 15, improving aerobic endurance significantly irrespective of weekly duration.

Paper 4.

- The Borg scale was safe and adhered to when prescribing and monitoring 12 months of self-administered balance and resistance exercise.
- The Borg scale was efficacious when the prescribed RPE was kept between 13 and 17, improving balance and strength significantly irrespective of weekly duration.

Future perspectives

The RENEXC-trial is, to date, the largest exercise trial in patients with CKD, not on KRT. In future research it would be of interest to perform a larger multicenter study examining the effect of self-administered, individualised, long-term exercise in patients with CKD not on KRT, to strengthen the evidence for this type of exercise intervention.

Future studies could explore how to incorporate new technology to facilitate exercise follow up, monitor progression and to increase exercise adherence to self-administered exercise in the long-term.

The studies in this thesis did not explore whether exercise frequency had any association with improvements in physical performance. As knowledge regarding how exercise frequency affects physical performance is limited, this could be considered in future research.

As balance exercise has been examined in a limited number of studies, future research should further explore balance as an exercise intervention in patients with CKD.

As the knowledge of exercise effects on HRQOL in patients with CKD not on KRT is limited, future research should further examine the effects of exercise interventions on PROMs in patients with CKD not on KRT. It would be of interest to increase understanding from a patient perspective of what changes are perceived as meaningful after an exercise intervention with a qualitative study.

It would be of interest to increase understanding from a patient perspective of self-administered exercise prescribed and self-monitored with the Borg scale with a qualitative study.

Future studies could investigate the use of the Borg scale for prescribing and monitoring exercise intensity for balance exercise, to evaluate the validity and applicability of the method in balance exercise.

Future studies could investigate the psychometric properties of the outcome measures included in the test-battery used at the Kidney Department at Skåne University Hospital, to strengthen the accuracy of the clinical assessments and research findings.

Finally, it would be valuable to initiate an international cooperation to establish exercise recommendations based on the current state of the research field, regarding exercise prescription (frequency, intensity, type, time, progression, and volume) and exercise setting, laying the foundations for updated guidelines for exercise in patients with CKD.

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Popular summary

Chronic kidney disease (CKD) is a global health problem, affecting around one in ten people. The kidneys play a central role in the body, filtering the blood to remove waste products, regulating water balance, maintaining electrolyte- and acid-base balance, producing hormones and activating vitamin D.

When kidney function declines patients experience symptoms such as fatigue, bone and joint pain, loss of muscle strength, poor sleep, nausea, poor appetite, and physical inactivity. This results in a decline in aerobic endurance, balance and strength, which can affect the ability to perform activities in daily life. Furthermore, patients with CKD experience lower health-related quality of life compared to healthy individuals.

Physical activity is shown to have several health-benefits in patients with CKD but is not yet implemented into standard care in most countries. In general, current research is focused on patients in the later stages of kidney disease, when it is necessary to perform dialysis to clean the blood, and on exercise trials performed in in-centre under supervision of health-care personnel. However, it is not feasible to implement in-centre exercise for all patients with CKD due to the large number of affected patients. Few studies have examined self-administered exercise, and few have examined long-term exercise programmes.

There is a need for more knowledge about exercise in earlier stages of CKD, as well as for studying the effects of exercise during longer intervention periods in patients who represent clinical reality, i.e. also the elderly and multimorbid. The RENal EXerCise (RENEXC) trial was created to address this knowledge gap, focusing on a sustainable way to integrate exercise into the everyday life of people with CKD. All studies in this thesis are based on data from the RENEXC-trial.

It is essential that self-administered exercise can be performed in a safe yet efficacious way. However, little is known about the best method of prescribing and monitoring self-administered exercise intensity in patients with CKD.

The aims of this thesis were to investigate the effects of 12 months of self-administered, individualised exercise on physical performance and health-related quality of life and how exercise could safely and efficaciously be prescribed and monitored in patients with CKD 3-5.

In the RENEXC-trial we used The Borg Rating of Perceived (RPE) exertion scale to prescribe and monitor exercise intensity. The Borg scale is a subjective scale where each individual rates their perception of the level of exertion during a physical activity. The scale ranges from 6 to 20, where 6 corresponds to no exertion at all, and 20 corresponds to maximal exertion. In patients with CKD, the Borg scale has been used to prescribe aerobic exercise, and in some studies resistance exercise, but to our knowledge, no studies have examined the use of the Borg scale in balance exercise.

Adults with CKD, not treated with dialysis or a kidney transplant, at the Kidney Department at Skåne University Hospital in Lund, Sweden, were invited to participate in the RENEXC-trial. The inclusion criteria were open, if participation in exercise did not pose a risk to the patient’s health. We included a total of 151 patients in the study, making the RENEXC-trial the largest exercise trial in patients with CKD that are not yet on dialysis.

The patients were randomised to perform either balance or resistance exercise. All patients performed aerobic endurance exercise. Exercise intensity for the aerobic endurance exercise was prescribed to be “somewhat hard to hard”, with a RPE of 13-15 on the Borg scale. The exercise intensity for balance and resistance exercise was prescribed to be “somewhat hard to very hard”, with a RPE of 13-17 on the Borg scale. The goal for the weekly duration of aerobic endurance exercise was 60 minutes, and 90 minutes for balance or resistance exercise, totalling 150 minutes per week. All exercise programmes were individualised, according to randomisation group, each patient’s physical performance at the start of the study, and each patient’s preferences and individual goals. Patients were instructed on how to perform their exercise programme by the research physiotherapist at the start of the study and could choose to perform the exercise at home or at a gym. The patients documented the performed exercise in an exercise diary, noting exercise intensity for each exercise using the Borg RPE scale and the duration of each exercise session in number of minutes. The exercise diary was sent to the research physiotherapist at regular intervals.

The research physiotherapist performed follow up via phone contact, once per week during the first three months of the study and every second week for the remaining nine months. The exercise programme was continually adjusted according to each patient’s progression, maintaining exercise intensity within the prescribed RPE and increasing exercise duration to reach the goal of a total of 150 minutes per week. Follow up and monitoring progression was performed via phone contact, during the visits to the clinic after four, eight and twelve months of exercise.

Physical performance (evaluated with several measures of aerobic endurance, balance, strength and fine motor skills) and health-related quality of life (evaluated by each patient with a questionnaire), were assessed at the beginning of the study, and after four, eight and twelve months of exercise.

In paper 1 of this thesis, both balance and resistance exercise, combined with aerobic endurance exercise, significantly improved or maintained all measures of physical performance. There was no difference between the exercise groups.

In paper 2, patients who performed resistance exercise in combination with aerobic endurance exercise had greater improvements in health-related quality of life over the 12 months of exercise compared with the patients who performed balance exercise in combination with aerobic endurance exercise. However, both exercise groups maintained most aspects of health-related quality of life, indicating that both balance and resistance exercise, combined with aerobic endurance exercise, could contribute to maintaining health-related quality of life in patients with CKD.

In papers 3 and 4, we registered a high adherence to the exercise programme and that most patients were able to perform aerobic endurance, balance, and resistance exercise within the prescribed exercise intensity. Results showed that the prescribed exercise was safe to perform self-administered. There was a wide variation in the number of minutes of exercise performed per week. In paper 3, we found that patients with lower aerobic endurance capacity at study start managed to perform less minutes of aerobic endurance exercise per week. However, there was no association between the number of minutes exercised per week and the change in physical performance. This means that the patients could improve aerobic endurance, balance, strength irrespective of the weekly duration of exercise when exercise intensity was maintained within the prescribed RPE.

In conclusion, 12 months of self-administered, individualised exercise significantly improved or maintained physical performance and maintained health-related quality of life in both groups. The Borg scale was a safe and efficacious method for prescribing and monitoring self-administered, individualised exercise in patients with CKD, resulting in high adherence to the exercise prescription and long-term sustainability. Regular contact with a physiotherapist most likely facilitated adherence.

The findings of this thesis contribute to increased knowledge on how exercise can be prescribed and monitored in a safe and efficacious way in a patient’s home or at a gym. The Borg RPE scale facilitates adherence showing that regular exercise is sustainable for a longer period of time in patients with CKD not on kidney replacement therapy.

Populärvetenskaplig sammanfattning

Kronisk njursvikt (CKD) är ett globalt hälsoproblem som drabbar cirka en av tio personer. Njurarna har en central roll i kroppen genom att filtrera blodet och avlägsna slaggprodukter. Njurarna reglerar kroppens vätskebalans, salt- och mineralbalansen samt syra-basbalansen. Njurarna producerar även hormoner och aktiverar vitamin D.

När njurarnas funktion försämras upplever patienterna flera symptom såsom fatigue, smärta i skelett och leder, förlust av styrka, dålig sömn, illamående, nedsatt aptit och fysisk inaktivitet. Detta resulterar i en nedsatt kondition, balans och styrka, vilket kan påverka möjligheten att utföra aktiviteter i det dagliga livet. Personer med CKD har även sämre hälsorelaterad livskvalitet jämfört med friska individer.

Träning och fysisk aktivitet har visats ha flera goda effekter på hälsan hos patienter med CKD, men på många ställen i världen ingår inte träning i standardbehandlingen av denna patientgrupp. Merparten av forskningen fokuserar på patienter i senare delar av njursjukdomen, när blodet behöver renas genom dialys, och på träningsinterventioner som utförs på sjukhus, övervakat av hälso- och sjukvårdspersonal. Dock är det inte möjligt att erbjuda träning på sjukhuset för alla patienter med CKD. Det saknas studier som undersöker självadministrerad träning, och träning som pågår under en längre tid.

Det finns ett behov av mer kunskap kring träning i tidigare stadier av CKD, samt kring effekten av längre träningsinterventioner hos patienter som representerar den kliniska verkligheten, det vill säga äldre och multisjuka personer.

Målet med denna avhandling var att undersöka effekterna av självadministrerad, individanpassad träning på fysisk förmåga och hälsorelaterad livskvalitet och hur träning under en längre tidsperiod kunde förskrivas och följas med Borgskalan.

RENal EXerCise (RENEXC) studien skapades för att adressera denna kunskapslucka, och fokuserade på ett hållbart sätt att integrera träning i vardagen hos patienter med CKD. Alla delstudier i denna avhandling baseras på RENEXC-studien.

När träning utförs självadministrerat är det viktigt att den både är säker att utföra, samt att den är effektiv. Det saknas kunskap kring hur träningsintensitet bör förskrivas och följas vid självadministrerad träning hos patienter med CKD. I RENEXC-studien valde vi att använda Borgsskalan för att förskriva och följa träningsintensitet. Borgskalan Rating of Perceived Exertion (RPE) är en subjektiv skattningsskala där en individ självskattar sin upplevda ansträngning under fysisk aktivitet. Skalan går från 6, motsvarande ”ingen ansträngning alls”, till 20, motsvarande ”maximal ansträngning”. Borgskalan har använts för att förskriva konditionsträning, och till viss del för styrketräning hos patienter med CKD. Det finns till vår kännedom inga studier som har undersökt användningen av Borgskalan hos patienter med CKD eller användningen av Borgskalan för att förskriva träningsintensitet för balansträning.

Vuxna med CKD, som inte påbörjat dialysbehandling och inte hade ett njurtransplantat vid njurmottagningen på Skånes universitetssjukhus i Lund, erbjöds att delta i RENEXC-studien. Inklusionskriterierna hölls öppna, förutsatt att patientens medverkan i träning inte utgjorde någon risk för individens hälsa. Vi inkluderade 151 patienter i studien, vilket innebar att RENEXC-studien är den största träningsstudien för patienter med CKD som ej är i dialysbehandling.

Patienterna randomiserades till att utföra antingen balans eller styrketräning. Alla patienter utförde även konditionsträning. Konditionsträningen förskrevs till att vara ”något ansträngande till ansträngande”, RPE 13–15 på Borgskalan. Träningsintensiteten för balans och styrketräning förskrevs till att vara ”något ansträngande till mycket ansträngande”, RPE 13–17 på Borgskalan.

Målet var att patienterna skulle utföra 60 minuter konditionsträning och 90 minuter balans- eller styrketräning, totalt 150 minuter per vecka. Alla träningsprogram individanpassades utifrån randomiseringsgrupp, patienternas fysiska förmåga vid studiens start samt individuella preferenser och mål. Patienterna instruerades i hur träningsprogrammet skulle utföras vid studiens start, och de kunde välja mellan att utföra träningen hemma eller på ett gym. Träningsintensitet för varje övning och träningens duration i minuter dokumenterades i en träningsdagbok som skickades till forskningsfysioterapeuten med regelbundna intervall.

Forskningsfysioterapeuten följde upp träningen via telefonkontakt, varje vecka de första tre månaderna av studien och därefter varannan vecka under resterande nio månader. Träningsprogrammet justerades kontinuerligt utifrån varje patients progression, med mål att bibehålla träningsintensiteten inom den förskrivna ramen för RPE och att öka träningsdurationen till totalt 150 minuter per vecka. Uppföljning och progression av träningsprogrammen skedde främst via telefon, men ytterligare justeringar skedde vid de kliniska besöken efter fyra, åtta och tolv månaders träning.

Fysisk förmåga (utvärderat med flera mätinstrument för kondition, balans, styrka och finmotorik) och hälsorelaterad livskvalitet (utvärderat med en enkät) bedömdes vid studiens start och efter fyra, åtta och tolv månaders träning.

I delstudie 1 förbättrade både balans- och styrketräning kombinerat med konditionsträning, alla aspekter av fysisk förmåga. Det fanns ingen skillnad mellan träningsgrupperna.

Delstudie 2 visade att de patienter som tränade styrketräning kombinerat med konditionsträning uppvisade större förbättringar i vissa aspekter av hälsorelaterad livskvalitet jämfört med de patienter som tränat balansträning kombinerat med konditionsträning. Dock var de flesta aspekter av hälsorelaterad livskvalitet bibehållen i båda grupperna.

Delstudier 3 och 4 visade hög följsamhet till träningsprogrammen, och att majoriteten av patienterna kunde genomföra konditions-, balans- och styrketräning enligt den förskrivna träningsintensiteten. Träningen var säker att genomföra då inga träningsrelaterade skador rapporterades under studietiden. Vi fann en stor variation i antalet tränade minuter per vecka för alla typer av träning. I delstudie 3 utförde patienter med lägre kondition vid studiens start färre minuter konditionsträning per vecka. Det fanns däremot ingen association mellan antalet tränade minuter per vecka och förändringen i fysisk förmåga, vilket tyder på att träningen kunde förbättra kondition, balans, och styrka, oavsett med vilken duration den utfördes när träningsintensiteten låg inom den förskriva ramen.

Sammanfattningsvis, visade RENEXC-studien att träningsprogrammen var säkra och effektiva, med signifikanta förbättringar i eller bibehållen fysisk förmåga och bibehållen eller förbättrad hälsorelaterad livskvalitet. Borgsskalan var en säker och effektiv metod att förskriva och följa träningsintensitet vid självadministrerad träning hos patienter med CKD. Den bidrog till hög följsamhet till träningsförskrivningen och en långsiktig hållbarhet. Regelbunden kontakt med en fysioterapeut underlättade säkerligen följsamheten.

Resultaten i denna avhandling bidrar till ökad kunskap kring hur träning kan förskrivas och utföras självadministrerat på ett säkert och effektivt sätt. Denna avhandling visar hur Borgskalan kan bidra till hållbar och långsiktig träning hos patienter med CKD som inte påbörjat dialys.

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