Published in final edited form as:

Am J Kidney Dis. 2017 June ; 69(6): 837–852. doi:10.1053/j.ajkd.2017.01.051.

Exercise and CKD: Skeletal Muscle Dysfunction and Practical Application of Exercise to Prevent and Treat Physical Impairments in CKD

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Abstract

Patients with chronic kidney disease (CKD) experience substantial loss of muscle mass, weakness and poor physical performance. As kidney disease progresses, skeletal muscle dysfunction forms a common pathway for mobility limitation, loss of functional independence, and vulnerability to disease complications. Screening for those at high-risk of mobility disability by self-reported and objective measures of function is an essential first step in developing an interdisciplinary approach to treatment which includes rehabilitative therapies and counseling on physical activity. Exercise has beneficial effects on systemic inflammation, muscle and physical performance in CKD. Kidney health providers need to identify patient- and care delivery barriers to exercise in order to effectively counsel patients on physical activity. A thorough medical evaluation and assessment of baseline function using self-reported and objective function assessment is essential to guide an effective, individualized exercise prescription to prevent function decline in persons with kidney disease. This review focuses on the impact of kidney disease on skeletal muscle dysfunction in the context of the disablement process and reviews screening and treatment strategies that kidney health professionals can employ in clinical practice to prevent functional decline and disability.

Keywords

Kidney disease; Physical function; Muscle; Exercise; Prevention; Frailty; CKD; ESRD; Older Adults; Muscle Dysfunction; Recommendations

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Case presentation

A 68 year-old obese man with chronic kidney disease (CKD) stage 3b-4 due to diabetes comes to clinic for follow-up. His estimated glomerular filtration rate (eGFR) 3 months ago was 35ml/min per 1.73m² and his blood sugars are controlled with 20 units of glargine insulin nightly, and he does not report any symptomatic hypoglycemia. His blood pressure and volume are controlled with furosemide 40mg daily, amlodipine 10mg daily, and lisinopril 40mg daily.

When asked about his physical activity, the patient states that he is not exercising regularly. He says he is relatively inactive and walks with the assistance of a cane. He does not report having fallen but says that over the last 6 months he has lost his balance on several occasions. He does not have stairs in his house, and he uses a walk-in shower without difficulty. He notes that it is now harder for him to clean his house and to work in the garden, and he often suffers significant muscle fatigue after performing household chores. He does not report any lightheadedness, any shortness of breath or chest pain limiting his activity.

Kidney disease and muscle dysfunction

Overview

This common presentation highlights the need for nephrologists to understand the burden of kidney disease on functional impairments and the disablement process. Patients with CKD have lower physical function^{1,2} and impaired physical performance,³ contributing to a high prevalence of frailty⁴ and mobility disability^{5,6} and an increased risk of mortality. The gerontological model of the disablement process helps contextualize the role of CKD-associated muscle impairment in functional decline⁷. This model operationalizes the steps to disability so that specific assessments can clearly be classified as to where they fit in the pathway from muscle impairment to disability. Muscle impairment is defined by physiologic dysfunction and structural abnormalities such as atrophy, reduced strength or reduced endurance⁸. Early recognition of skeletal muscle impairment through screening of objective lower extremity physical performance and self-reported functional limitation helps identify patients at high risk of functional decline and disability. Functional limitations manifest either as objective limitations in performing basic physical performance tasks (i.e. gait speed, timed up and go (TUG)) that comprise the building blocks necessary for independent function or as self-reported mobility limitation (i.e. difficulty walking ¼ mile or ascending 10 steps). Early referral to rehabilitative therapy and initiation of an individualized exercise program may improve exercise tolerance and physical performance, helping prevent functional decline, mobility disability, and frailty. This review focuses on the interplay of kidney disease with skeletal muscle dysfunction and the disablement process, discussing screening and treatment strategies that kidney health professionals can employ in clinical practice to prevent functional decline and disability.

Dysregulation of mitochondrial metabolism

Reduced kidney function leads to the retention of uremic solutes culminating in inflammation, oxidative stress and insulin resistance⁹ promoting skeletal muscle dysfunction. Skeletal muscle serves as a putative target of chronic kidney disease, with the kidney disease milieu, including inflammation and hypercatabolism, resulting in reduced strength, physical performance and physical function. Left unabated, skeletal muscle dysfunction forms the common pathway for mobility disability, loss of functional independence, and further vulnerability to major disease complications.

Impaired skeletal muscle mitochondrial metabolism is a sentinel pathologic event in the disablement process among patients with kidney disease. Inefficient muscle mitochondrial metabolism is characterized by oxidative stress, insulin resistance¹⁰ and impaired lipid metabolism¹¹. Mitochondrial oxidative stress, an indicator of muscle mitochondrial dysfunction, activates proteolytic pathways promoting muscle atrophy^{12,13}. Furthermore, among older adults lower mitochondrial metabolic capacity and efficiency is linked to reduced mobility and exercise intolerance^{14,15}.

Chronic kidney disease is associated with impaired muscle mitochondrial metabolism^{16–18} and mitochondrial oxidative stress¹⁹. The advent of non-invasive functional ³¹P Magnetic Resonance Spectroscopy (³¹P MRS) and optical spectroscopy (OS) provides a window into early alterations of *in-vivo* muscle mitochondrial energetics among patients with kidney disease. Recently a study of non-diabetic patients with advanced CKD and preserved lower extremity physical performance demonstrated substantial reductions in coupling efficiency of muscle mitochondria defined by the amount of ATP (ATP_{flux}) generated per unit of oxygen consumption (O₂uptake) (or P/O ratio) compared with healthy controls²⁰ (Figure 1). This lower mitochondrial coupling efficiency is primarily characterized by an increased consumption of oxygen to maintain ATP_{flux} through the electron transport chain. Uncoupling of oxidative phosphorylation (lower P/O) is an indicator of redox stress^{21,22} and may reflect insertion of uncoupling channels in the inner mitochondrial membrane in response to heightened oxidative stress in patients with advanced CKD. The substantial reduction in mitochondrial efficiency among patients with CKD with preserved strength compared to predicted values indicates that reduced muscle mitochondrial quality may presage declines in exercise efficiency and tolerance²³. Indeed, among patients with kidney failure requiring long-term hemodialysis, there is substantially reduced mitochondrial volume density in muscle and increased plasma isofuran levels, indicative of mitochondrial oxidative stress¹⁹. A recent detailed mechanistic study in a murine model of CKD demonstrated that reductions in mitochondrial content and function precedes loss of muscle strength and physical endurance²⁴. In summary, recent studies reveal muscle mitochondrial disruption as a novel pathophysiologic mechanism contributing to the high prevalence of physical impairments in individuals with CKD.

Assessing muscle function in CKD

Defining skeletal muscle dysfunction: sarcopenia and dynapenia

The Foundation for the National Institutes of Health Sarcopenia project recently established a clinical paradigm for clinicians making a differential diagnosis of poor physical function based on empirical evidence²⁵. Definitions of sarcopenia relying on estimates of lean mass alone are inconsistently associated with mortality and mobility disability in both older adults²⁶ and people with kidney disease²⁷. Although sarcopenia has been emphasized as leading to dynapenia (muscle weakness), a more appropriate focus would be the central function of muscle, which is providing force for body movements and actions. As such, mobility is perhaps the best way to evaluate muscle impairments and serves as a primary indicator of functional ability.

Screening for muscle function impairments and functional limitations, critical intermediates in the disablement process (Figure 2), is a rapid and cost-effective approach to identify patients with kidney disease at high risk of frailty, mobility disability and mortality^{27–29}, and most individuals who screen positive for functional limitation or frailty would benefit from referral to physical rehabilitative therapies to improve confidence, strength and function prior to initiation of an exercise regimen.

Muscle impairment and functional limitations

Low glomerular filtration rate (GFR) is associated with marked muscle impairment³⁰ and heightened risk of functional limitations.³¹ A recent investigation in older adults demonstrated that lower kidney function assessed by measured creatinine clearance was associated with reduced calf muscle density coinciding with consistently lower usual gait speed and more rapid declines in quadriceps muscle strength over time (figure 3)³². Lower muscle density may reflect accumulation of intermuscular fat and reduced muscle quality. Weak grip or quadriceps strength are accepted measures of muscle impairment strongly associated with functional limitation, and mobility disability in community dwelling older adults^{26,33} and greater risk of mortality among patients with CKD²⁹

Quadriceps muscle endurance is another measure of sarcopenia associated with functional limitations in older adults.^{33,34} A more recent study of older adults investigated the association of quadriceps muscle endurance and quadriceps maximal strength with persistent and severe mobility limitation³⁵. Persistent and severe mobility limitation was defined as new onset of self-reported persistent severe difficulty with ambulating ¼ mile or ascending 10 steps on two occasions separated by 6 months. Quadriceps muscle endurance was estimated from the total isokinetic work performed over 30 knee extension repetitions while maximal quadriceps strength was estimated by the maximum of 3 isometric contractions. Both muscle endurance measured by isokinetic work and muscle strength were independently associated with persistent and severe mobility limitation. The association of muscle endurance with persistent and severe mobility limitation was independent of maximal strength suggesting that muscle endurance testing may reveal vulnerability to functional decline beyond strength testing. Furthermore, greater quadriceps muscle quality assessed by total isokinetic work and maximum strength normalized to leg lean mass was

strongly associated with lower risk of persistent severe mobility limitation after adjusting for demographics, body size, and eGFR_{cysc}³⁶ (figure 4). These associations were similarly observed in the 186 participants with CKD (defined by eGFR_{cysc}<60ml/min per 1.73m²)³⁶. Unfortunately, the use of isokinetic dynamometers may be cost prohibitive for application in the clinic setting. As an alternative, low cost functional tests integrating muscle endurance and strength such as the 30-second chair stand test have been employed in CKD³⁷ with the added benefit that reference data to define below average performance exist for these tests^{37A}.

Functional limitations are defined as restrictions in basic physical actions (e.g. ambulation, grasping, climbing stairs). Mobility limitation is often the first manifestation of functional limitation and functional decline. Functional and mobility limitations are critical links between muscle impairment and disability defined as difficulty or inability to perform life activities (Figure 2). Mobility limitations can be assessed by self-report or objectively by physical performance testing, providing complementary insight into disease burden on functioning³⁸. Questions probing self-reported modifications in performing mobility tasks are particularly helpful in screening preclinical mobility disability and functional limitations. Preclinical mobility disabilities are defined as limitations that only exist in challenging environments and increase risk for mobility disability^{39,40}. Assessment of preclinical mobility disability is particularly important in patients with CKD given the particularly high risk of declines in mobility^{6,41}. Several screening questions have been proposed to assess preclinical mobility disability (box 1)⁴².

Box 1

Assessment of functional limitation and mobility limitation in nephrology clinic setting

Screening questions: Self-reported mobility limitation^{39,41}

1. “Do you have difficulty walking ¼ mile or climbing up 10 steps?”
2. “Have you changed the way you walk ¼ mile (about 2–3 city blocks), or how often you do this, due to a health or physical condition?”

Objective assessment of mobility: Physical performance assessment in clinical setting (Table 1).

1. Usual gait speed (3-meters distance is adequate): <0.8m/s associated with death in CKD patients²⁹. 1m/s associated with improved survival across multiple populations⁴³.
2. Timed up and go test (4 meter distance is adequate): 12 seconds associated with death in CKD patients.
3. Short physical performance battery: <8¹⁰⁵ associated with increased risk of mobility disability in the general population.

Source: Brown & Flood⁴².

Tests of physical performance, such as gait speed, TUG, and the short physical performance battery (SPPB), are objective measures of functional limitations strongly associated with mobility disability and death across multiple populations^{43,44}(Table 1). Across the spectrum of CKD, worse lower extremity physical performance is strongly associated with mortality^{28,29}. In particular, usual gait speed measurement is objective, easy to measure, reproducible, and strongly associated with mortality, falls, and activities of daily living disability in patients with CKD²⁸. Recommendations for implementing gait speed assessment into nephrology clinical practice have previously been comprehensively reviewed⁴⁵. Mobility limitation measured by slow gait speed and muscle impairment (weakness) are both critical objective components of the geriatric syndrome referred to as frailty.

Frailty

Frailty is defined as a clinical syndrome of vulnerability traditionally characterized by weak grip strength (muscle impairment), slow gait speed (physical performance), low physical activity, low energy, and weight loss⁴⁶. The presence of 3 or more of these characteristics is requisite for frailty. The frailty phenotype is strongly associated with disability, hospitalization and mortality across multiple populations^{47–51}. The frailty syndrome has been operationalized in several different ways in the kidney disease population and all are strongly associated with mortality^{52–54}. Among older adults and patients with CKD, lower kidney function is associated with greater risk of frailty^{4,55}. Importantly, frailty among patients with CKD has been associated with increased risk of death or dialysis initiation⁴.

The most modifiable component of the frailty phenotype in patients with kidney disease is physical inactivity⁴. Interventions that increase physical activity may act as a model for preventing or mitigating frailty,⁵⁶ while declines in physical activity predict, early on, the development of the rest of the frailty phenotype by leading to the loss of physical function⁵⁷.

In summary, kidney disease is associated with substantial muscle impairment and functional limitation contributing to a high prevalence of frailty. Assessment of preclinical mobility disability and objective functional limitations is important for identifying those at high risk for frailty who would benefit from closer medical review and referral to physical therapists for improving strength and balance prior to initiating exercise. Figure 5 outlines one potential clinical algorithm providers can employ to identify high-risk CKD patients and target physical therapy interventions prior to initiation of exercise therapy. An understanding of a patient's functional status and use of an interdisciplinary approach involving rehabilitative therapies to address functional limitations is vital to providing a feasible, safe, and individualized exercise prescription.

Evidence for the benefit of exercise

Mechanisms of improvement in muscle performance

Studies of aerobic exercise training in the general population demonstrate multiple potential mechanisms underlying exercise-associated improvements in muscle performance. Muscle mitochondrial energetic inefficiency may be an important factor in exercise intolerance and

reduced muscle performance²³, and exercise has been shown to improve the efficiency of muscle mitochondrial oxidative metabolism⁵⁸. These improvements appear important for generating and maintaining leg muscle power evidenced by studies of endurance training^{59,60}, and, interestingly, described improvements in the ability to maintain maximal muscle power (endurance) exceed changes in whole body aerobic capacity (VO_{2max})⁶⁰ (i.e. oxygen utilization). Furthermore the improvement in muscle power strongly correlates with changes in tissue oxidative capacity represented by increased muscle mitochondrial volume and muscle capillary fiber density⁶⁰.

Studies of exercise training in patients with CKD confirm substantial improvements in leg muscle size⁶¹ and power corresponding to morphologic changes in muscle capillary density⁶², improvements in oxidative metabolism⁶³, muscle mitochondrial biogenesis⁶⁴, and reduced systemic inflammation⁶⁵. A recent randomized cross-over study of hematocrit normalization and in-center cycling exercises among hemodialysis patients demonstrated substantial changes in muscle power (average 22% increase) and oxidative metabolism (mean 43% increase in citrate synthase activity) among the in-center cycling group but not the hematocrit normalization group⁶³. These changes in muscle power and oxidative metabolism coincided with less marked changes in whole body aerobic capacity (VO_{2max}) with exercise training. In contrast, more substantial changes in resting muscle-specific oxygen consumption coinciding with improvements in 6-minute walking distance were observed in a sub-study of the EXCITE trial, a home-based randomized controlled trial of walking exercise among dialysis patients⁶⁶. The change in muscle-specific oxygen consumption suggests possible improvements in muscle mitochondrial efficiency, either by increased muscle mitochondrial volume density or mitochondrial quality. These muscle-specific functional changes complement findings from a 12-week randomized trial of resistance exercise training in advanced CKD demonstrating increased muscle mitochondrial biogenesis measured by mitochondrial DNA copy number⁶⁴. Coinciding with the increase in mitochondrial DNA copy number was a reduction in systemic IL-6 level. These findings of an anti-inflammatory effect of long-term exercise in advanced CKD were more recently confirmed in a study of home-based walking exercise⁶⁵. In this study, 6 months of moderate intensity walking for at least 30 minutes daily five times per week resulted in substantial decline in the IL-6/IL-10 ratio.

Exercise and physical limitations in older adults

The Lifestyle Interventions and Independence for Elders (LIFE) multicenter randomized controlled trial, which randomized 1635 participants to a structured physical activity program versus an attention control intervention, is the gold standard trial for demonstrating the effectiveness of physical activity on reducing mobility disability risk among older adults with physical limitations⁶⁷. Although older adults with CKD were eligible, dialysis requiring kidney disease was excluded. Participants were eligible if they had physical limitation defined by low SPPB scores of 4–9 and sedentary lifestyle defined by

125minutes of total self-reported activity per week. The exercise intervention was individualized and gradually progressed to a goal of walking 30min/day, 10min/day of lower extremity strength training (ankle weights), and 10 min/day flexibility and balance training⁶⁸ and involved attendance at 2 center-based visits per week and home-based activity 3–4 times

per week for the duration of the study. The attention control group received regular health education workshops.

Among adults with a mean age of 79 years, average BMI of 30 kg/m² and SPPB of 7.4 followed for 2.6 years on average, the physical activity intervention was associated with a 28% reduction in risk of persistent mobility disability compared to health education. Recent cost-effectiveness analysis demonstrated that the improvement in quality adjusted life years (QALY) seen with the physical activity intervention was similar in magnitude to a Diabetes Prevention Program and lifestyle intervention⁶⁹.

Unfortunately, no studies targeting the CKD population have evaluated the effectiveness of exercise in reducing the risk of mobility disability. Furthermore no large published studies have used an attention control to account for the Hawthorne Effect associated with the extra attention and higher level of clinical surveillance in the intervention compared to the control. Nonetheless, smaller randomized trials of exercise in patients with CKD have demonstrated improvements in muscle strength, physical performance, and self-reported physical function⁷⁰.

Benefits of exercise in kidney disease

Several recent extensive meta-analyses have demonstrated benefits of short-term, supervised exercise on training on fitness (VO_{2peak}), sarcopenia (leg muscle mass, quadriceps cross-sectional area and strength), physical performance, self-reported physical function, and quality of life (QOL) among participants with advanced CKD, including dialysis dependent populations^{70–72}. Benefits were observed regardless of type of exercise.

The EXerCise Introduction to Enhance performance in dialysis patient trial (EXCITE) demonstrated the effectiveness of a 6-month personalized, home-based walking exercise program to improve walking capacity and muscle strength compared to “usual care”⁷³. This multicenter randomized, controlled trial in the dialysis population excluded participants with limited mobility or high degree of fitness (6 minute walk distance >550meters), exertional angina, or stage 4 NYHA heart failure. Participants engaged in a personalized home-based exercise program supervised by dialysis staff trained by a rehabilitation team. Exercise training involved gradual increased intensity of walking cadence using a low cost metronome. Baseline recommendations for walking cadence (speed or steps/min), partition of work and resting time, and number of repetitions were determined by performance on the 6-minute walk distance. During the 6 months of training 31% of participants withdrew from the exercise group compared with 15% from the placebo. In addition 47% of those who completed the study were designated as having low adherence to the protocol (<60% of sessions). Hospitalization was only reduced among those in the exercise group who had completed the trial compared to control patients who completed the trial, but not in the intent-to-treat analysis. Among those who completed the trial, there were meaningful and significant improvements in muscles strength and endurance compared to the control group. Furthermore there was a dose dependent effect with greater adherence associated with greater improvement in physical performance measures.

A major challenge in exercise programs is participant withdrawal and waning adherence over time, emphasizing the need for rehabilitative therapies prior to the initiation of structured exercise programs for high-risk patients and further underscoring the importance of long-term engagement and encouragement of patients during a prolonged, individualized exercise program. Although less common, long-term randomized trials of exercise in advanced CKD and dialysis patients have demonstrated the safety of exercise up to 12 months (Table 2), with the lack of serious adverse events associated with exercise in this population confirmed in a recent meta-analysis⁷⁰. Notably, this may be a consequence of restrictive eligibility criteria and implementation of screening exercise testing at baseline. Nonetheless, long-term structured and supervised exercise has benefits on self-reported function or physical performance and objective measures of exercise capacity and muscle performance (Table 2).

Implementation of exercise into clinical practice first requires providers to understand the barriers to exercise in patients with kidney disease. Effective engagement and counseling on an individualized exercise prescription requires addressing patient and clinic-related barriers to exercise.

Barriers to exercise in kidney disease patients

A number of factors that negatively influence physical activity behavior in CKD patients have been identified. While the vast majority of the data pertains directly to hemodialysis patients,^{74–93} similar barriers are present in non-dialysis CKD patients⁹⁴. These barriers can largely be divided into patient and structural factors.

Patient-related barriers

The most frequently cited impediments to exercise among CKD patients are poor physical function related to comorbid disease burden and psychological and logistical barriers. Specific symptoms related to these comorbid conditions include chronic pain, fatigue, poor physical function, and dyspnea, as well as co-morbid diseases like cardiovascular disease (CVD), diabetes, and muscle wasting^{75–77,79,83,89,92}. Cognitive and psychological barriers are also prominent, including a fear of falling, low motivation, depression, feelings of being a burden on the clinic staff, and poor exercise self-efficacy^{76–78,83,84,92}. Logistical barriers, such as limited access to exercise facilities, transportation problems, and schedule constraints are also frequently cited^{76–78,83,85,92}.

Structural barriers

Structural Barriers to exercise among non-dialysis CKD patients include lack of informational support, social interaction and support, and challenges in the physical environment⁹⁴. CKD patients often feel that exercise is not prioritized by their healthcare team and lack tailored advice and support from their healthcare professionals. Although, patients indicate that social interaction would be a beneficial component of an exercise program, they described a lack of peer support networks among kidney patients to help improve confidence and adherence. Finally, patients expressed a lack of knowledge

regarding affordable, local exercise facilities and requested practical guidance to help them access these facilities and incorporate them in to their daily routine.

Structural barriers to exercise among hemodialysis patients include a lack of resources for exercise and training among providers and dialysis staff regarding their roles in assessing and encouraging physical activity. Resistance training equipment is rarely available, and often too bulky or expensive^{74,78,84}. Moreover, few facilities have a dedicated exercise specialist to properly promote physical activity, leaving this burden to the medical staff, who may lack the motivation, time, training, or expertise^{78,83,87,88}.

National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines recommend that all dialysis patients should have their physical activity levels assessed and should be regularly counseled by the dialysis staff to increase their physical activity levels.⁹⁵ Despite this, many nurses and technicians indicate that they do not feel it is part of their job description to promote exercise,⁸⁷ and the lack of training and incentives to encourage participation supports their argument⁸⁸. Furthermore few nephrologists assess physical activity or counsel patients to increase activity.^{81,82} This disturbing trend extends even to dialysis patients with ischemic heart disease, as only about 10% are referred to cardiac rehab, despite the subsidized costs⁹⁶ and demonstrated survival benefits⁸⁶.

Some of these barriers may arise from discrepancies between patients and medical staff regarding perceptions about exercise. One survey demonstrated a discrepancy between a high level of patient reported interest in exercise (90%) and nephrologist⁷⁷ misconception of a lack of patient interest. In addition, dialysis clinic staff described their patients as having little interest in exercise^{81,83}. While most patients also believe they would achieve significant health-related benefits from increasing their physical activity levels,^{76,79,84,85} only 45% of clinic nurses believe that most patients would benefit from regular exercise⁸⁷. Physicians (40%) also appear to be much more concerned about the risks of exercise compared to patients (8%),⁷⁷ representing another barrier to promoting physical activity.

Further research is necessary to help guide practical implementation of a robust exercise program utilizing existing dialysis staff and resources. This research must address the culture at dialysis clinics and promote recognition of the importance of physical activity. Indeed, Patricia Painter^{87,88,97} has tirelessly promoted implementation strategies for decades, focusing in large part on changing the culture at dialysis clinics to recognize the importance of physical activity for these patients. This has included developing a wealth of educational materials, such as those published by the Life Options Renal Rehabilitation Advisory Council. These materials are freely available at <http://old.lifeoptions.org/catalog/pdfs/booklets/exercise.pdf>.

Individualized exercise prescription

Exercise guidelines for patients with CKD have been published providing excellent resources for health providers^{98–100}. Exercise training prescriptions should be individualized to the patient's physical function with an emphasis placed on regular engagement and

evaluation of progress. The cornerstones of an individualized exercise prescription include assessing baseline function with a health evaluation, and addressing potential safety concerns.

Health Evaluation

Patients should undergo a medical evaluation that includes a complete health history, physical examination, assessment of cardiovascular disease risk factors and an assessment of current physical function¹⁰¹. Physical performance should be assessed for the hemodialysis patient mid-week on a non-dialysis day¹⁰¹. Referral to cardiac rehabilitation is reimbursed by the Centers for Medicare and Medicaid Services for patients with either symptomatic heart failure (left ventricular ejection fraction < 35%), acute myocardial infarction within the preceding 12 months, coronary artery bypass surgery, stable angina pectoris, recent history of heart valve replacement, coronary stenting and heart or lung transplant⁹⁶.

Special attention should be given to patients using beta-blockers, calcium channel blockers or alpha-blockers. Patients receiving beta-blockers may have reduced submaximal and maximal exercise capacity underscoring the importance of using perceived exertion to monitor exercise intensity. Additionally patients on beta blockers may develop hypoglycemia when exercising in hot and humid environments, so patients should be instructed about reducing the exercise intensity and duration under these conditions¹⁰². Patients receiving vasodilators such as alpha blockers, calcium channel blockers, central alpha agonists (clonidine), nitrates and hydralazine may develop hypotension after exercising. In this situation the cool-down period should be prolonged¹⁰⁰.

Safety

A complete list of contraindications for exercise training in patients with CKD can be found elsewhere^{98,103}. Absolute contraindications include unstable coronary heart disease, decompensated heart failure, uncontrolled arrhythmias, severe pulmonary hypertension (mean pulmonary arterial pressure >55mm Hg), severe and symptomatic aortic stenosis, uncontrolled hypertension (>180/110), and aortic dissection¹⁰⁰. In patients treated with hemodialysis, exercise can be performed in the arm or leg with dialysis access once the access has healed but this limb should not be exercised during dialysis. Patients treated with peritoneal dialysis (PD) achieve higher levels of exertion when the abdomen is empty; however, this factor should not discourage exercise among PD patients who require daytime dwells. Some patients experience abdominal discomfort due to contact between the dialysis catheter and abdominal viscus; this can be addressed by keeping enough fluid in the peritoneum to allow for floating of the catheter for those without day dwells. In patients prone to hypoglycemia, glucose levels should be checked before and after exercise and they should have high glycemic index snacks readily available. Specialized evaluation and treatment prior to starting an exercise training program should be considered in patients with arrhythmias and history of uncontrolled high blood pressure. Exercise should be stopped if patients develop excessive shortness of breath, angina, severe headache or dizziness.

Exercise recommendation

In order to prescribe an exercise regimen, Koufaki et al. have suggested the use of the FITT principle: Frequency, intensity, time, and type⁹⁹. Exercise recommendations for patients with CKD are summarized in Tables 3 and 4. Briefly, patients should exercise 2 to 3 times per week at the beginning of the training; the frequency can then be increased to 3 to 5 times per week. Intensity should be tailored according to patient tolerance to exercise and should be gradually increased. The duration of exercise depends on the health and physical condition of the patient and, likewise, should be progressively increased. The type of exercise should include aerobic, resistance, and flexibility exercise. For patients who are at risk of falls, balance exercises should be recommended^{98,104}.

Conclusion

Persons with CKD suffer a high burden of muscle impairment contributing to functional decline and mobility disability. Screening patients with CKD using both self-reported and objective measures of physical function is an essential first step to guide an interdisciplinary approach to treatment which includes rehabilitative therapies and counseling on physical activity. Exercise improves muscle impairment, physical function, and physical performance across the spectrum of CKD. Kidney health providers need to identify patient- and facility-related barriers to exercise to effectively counsel on physical activity. A thorough medical evaluation and assessment of baseline function using self-reported and objective function assessment is essential to guide an effective, individualized exercise prescription to prevent function decline in persons with CKD.

Acknowledgments

We thank Drs. Kushang Patel and Daniel Lam for their review and editing of this article. *Support:* This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (K23-DK099442 to BR). This work was also supported by an unrestricted fund from the Northwest Kidney Centers (BR). *Financial Disclosure:* Dr. Baback Roshanravan has participated as an investigator for a clinical trial supported by Stealth Biotherapeutics, but reports receiving no consultant fees, speaking fees or honoraria from the company. The remaining authors declare that they have no relevant financial interests. *Peer review:* Evaluated by 3 peer reviewers, Deputy Editor Weiner, and Editor-in-Chief Levey.

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Figure 1.

Panel A: Non-diabetic CKD patients have lower muscle mitochondrial coupling (P/O) efficiency of mitochondrial oxidative phosphorylation. Panel B: Among non-diabetic CKD patients lower GFR is associated with lower P/O. P-values are adjusted for age. Reproduced from Roshanravan et al²⁰ with permission of Elsevier.

Figure 2.

CKD leads to muscle impairment promoting functional decline, mobility disability, and frailty. This figure represents CKD in the context of the Nagi disablement model.

Abbreviations: PCMD – preclinical mobility disability. Source: Newman & Cauley⁷.

Figure 3.

Left panel: Lower kidney function by measured creatinine clearance (Clcr) is associated with consistently lower gait speed throughout follow up among older adults. Right panel: Lower Clcr at baseline is also associated with more rapid decline in knee extension strength over time. Reproduced from Roshanravan et al³² with permission of Elsevier.

Figure 4.

Left panel: Lower specific quadriceps muscle endurance (specific work) is associated with increased risk of persistent and severe mobility limitation among older adults enrolled in the Health Aging and Body Composition study. Associations were consistent when restricted to those with CKD. Right panel: Lower quadriceps maximal isometric strength (specific torque) is associated with increased risk of persistent and severe mobility limitation among older adults. Associations were consistent when restricted to those with CKD. Models are adjustment for age, sex, race, education, height, weight, study site, and eGFRcysc. Source: Roshanravan et al³⁶. Adapted from Roshanravan et al³⁵ with permission of Oxford University Press.

Figure 5.

Algorithm for two-step screening of functional impairments among high-risk patients with CKD and early referral for rehabilitative therapies prior to initiation of exercise. Source: Brown and Flood⁴². Abbreviations: SPPB – short physical performance battery, CV- cardiovascular, MS – musculoskeletal, Neuro – neurologic, PT – physical therapy.

Table 1

Measures of physical performance, strength, and endurance and their association with outcomes.

Test	Task	Population	Cut-points	Association with outcome	Studies	Resources
Physical performance						
Gait speed	Usual walking speed over 3, 4, 7, or 20 meters.	CKD; ESRD; older adults	<1m/s; <0.8m/s; <0.6m/s (dialysis)	Mortality: Each 0.1m/s slower associated with 12% higher risk of death in older adults and 26% higher in CKD	*Roshanravan ²⁹ , *Kutner ²⁸ , Studenski ⁴³ , Afalo ¹⁰⁶	Normative data ¹⁰⁷ ; normograms for life expectancy by age and speed available ⁴³ ; normograms for incident disability by age and gait speed ¹⁰⁸
Timed up and go (TUG)	Get up from seated position, walk 4 meters and return to seated position; (Tests balance, walking ability, fall risk)	CKD; older adults	12 seconds	Mortality: 81% greater risk if 12 seconds or slower; 8% for each 1 second slower; associated with falls in older adults	Roshanravan ²⁹ ; Shumway-Cook ¹⁰⁹ ; Wang ¹¹⁰	https://www.cdc.gov/steady/pdf/tug_test-a.pdf ; normative data ¹¹¹
Short Physical Performance Battery (SPPB)	Test of lower extremity function combining scores from usual gait speed and timed tests of balance and chair stands; score ranges from 0–12	Older adults	8 ¹⁰⁵ ; <10 ¹¹² ; small meaningful change is 0.5 point ¹¹³ ; substantial change is 1 point ¹¹³	ADL disability; mobility disability; death in older adults	Guralnik ^{44,114} ; Minneci ¹¹⁵	https://www.irp.nia.nih.gov/branches/leps/sppb/index.htm
6-minute walk distance (6MWD)	Maximal distance covered over 6 minutes; test of functional exercise capacity	CKD; ESRD; COPD; older adults	Poor exercise capacity<350 meters ¹¹⁶ ; clinically important difference of 50 meters	Mortality: <350meters associated with 2.82 fold increased risk of death in CKD; 11% reduction in risk of mortality for every 20 meters greater 6MWD in ESRD	*Roshanravan ²⁹ ; Veronese ¹¹⁷ ; Polkey ¹¹⁸ ; *Torino ¹¹⁹	Normative data ¹²⁰
400meter walk test	Time to walk 400 meters as quickly as possible	Older adults	Minimum clinically important difference is 28 seconds ¹²¹	Each additional 1-minute associated with 29% increased risk of mortality and 52% increased risk of mobility limitation	Newman ¹²²	
Strength/Endurance						
Grip strength	Maximal grip strength using dynamometer from dominant hand or hand on non-fistula arm	CKD; ESRD; older adults	CHS (Gender and BMI based) ¹⁶ ; FNIH (males<26kg, females<16kg) ²	Mortality: Weak grip associated with 79% increased risk of death in incident dialysis patients ²⁷	*Roshanravan ²⁹ ; *Isoyama ²⁷	Normative data ¹²³
Quadriceps Endurance	Total work performed over 30 knee extension repetitions using isokinetic dynamometer	Older adults; CKD	Lowest sex-specific tertile (men<1075 Joules, women<682 Joules)	Persistent and severe lower extremity limitation (PSLL): lowest sex-specific tertile associated with 29% greater risk of PSLL compared to highest tertile; mortality: lowest sex-specific tertile associated with 49% increased risk of death compared to highest tertile	Roshanravan ³⁶	
Quadriceps Strength	Maximum isometric strength (maximum of 3 attempts)	Older adults; CKD	Lowest sex-specific tertile (men<124 Nm, women<73 Nm)	PSLL: lowest sex-specific tertile associated with 38% increased risk of PSLL compared to highest tertile; mortality: lowest sex-specific tertile associated with 19%	Roshanravan ³⁶	

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Test	Task	Population	Cut-points	Association with outcome	Studies	Resources	
				increased risk of death compared to highest tertile			

Abbreviations: PSL- persistent severe lower extremity limitation; CKD, chronic kidney disease; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; CHS, Cardiovascular Health Study; BMI, body mass index; FNHI, Foundation for the National Institutes of Health; ADL, activities of daily living.

Table 2
Randomized controlled trials of exercise in kidney disease of at least 10 months duration

Study	Population	Intervention/control	Results	Monitoring	Adherence/Adverse Events
Leehey et al, 2016 ⁵	Obese diabetic patients with CKD 2–4 (n=36)	Intervention: 12 weeks of supervised exercise training (3x/wk) followed by 40 weeks of supervised home exercise + diet intervention; aerobic 3x/wk (60 minutes); resistance 3x/wk (20–30 min); Control: dietary counseling at baseline and 9 follow-up telephone calls	Walking capacity (treadmill time) at 12 wks compared to control (-4.3min vs -0.2 min; P=0.03); effect of exercise not significant after 52 weeks (P=0.14)	Intervention: Weekly phone calls and encouraged to meet with trainer once monthly; control: 9 follow-up telephone calls	4 lost to follow-up in exercise and 0 in control; no serious adverse events
Howden et al, 2015 ¹²⁴	CKD 3–4, plus >1 uncontrolled cardiac risk factor (n=83)	Intervention: 12 months aerobic and resistance based on ACSM guidelines; aerobic 5x/wk (moderate intensity >30min); resistance 2x/wk (moderate intensity); Control: usual care	6 minute walk distance of 54 meters after 12 months (vs -3m in control); preserved grip strength (P=0.03); preserved timed up and go (P=0.07); VO _{2peak} ; Exercise capacity (METs); Self reported physical activity	Nurse practitioner follow-up at 1 month to monitor impact of exercise on BP, blood glucose; exercise physiologist assessed BP and blood glucose levels (in DM) prior to gym session	70% adherence; 3 lost to follow-up and 1 discontinued in intervention group; 3 lost to follow-up and 3 discontinued in control; no serious adverse events
Greenwood et al, 2015 ¹²⁵	Stage 3–4 CKD (n=20)	Intervention: 12 month of aerobic and resistance training, 3x/wk (2x/wk supervised, 1x/wk home); aerobic exercise (recumbent stationary bike) with intensity of 80% heart rate reserve (from exercise testing); resistance training 80% of 1 repetition maximum (goal of 3 sets of 8–10 repetitions); Control: usual care	VO _{2peak} ; primary outcome, improved kidney function; secondary outcome, decreased pulse wave velocity	40-minute session with renal physiotherapist at baseline to discuss exercise and personal goals; weekly phone calls to encourage self-managed exercise and assess RPE	79% adherence; 2 training group dropped out (1 started PD and 1 emigrated); no serious adverse events noted
Kouidi et al, 2009 ¹²⁶	ESRD on dialysis (n=63); excluded diabetes	Intervention: 10 month supervised in-center aerobic and resistance exercise; aerobic in-center cycling during dialysis 3x/wk 90 minutes per session during first 2 hours of HD; target RPE of 13 out of 20 on borg scale; heart rate on exercise 60–70% of maximum; isometric & isotonic resistance exercise of abdomen and lower limbs 30 minutes while in seated position gradual increase to 3 sets of 15 repetitions per exercise with goal RPE of 13; Control: not specified	Exercise time; VO _{2peak} ; Left Ventricular Ejection Fraction; improved heart rate variability	2 exercise trainers specialized in physical rehabilitation supervised training sessions; continuous heart rate monitoring telemetrically during exercise	88.3% adherence; 59 completed study (2 discontinued in training and 2 lost to follow-up in control); no complications
Ouzouni et al, 2009	ESRD on dialysis (n=35); excluded diabetes	Intervention: 10 month supervised aerobic and resistance training during first 2hr of dialysis; aerobic cycling exercise for 30 minutes targeting RPE of 13–14 on Borg scale; resistance exercise for abdominal and lower limb muscles; Control: not specified	Exercise time; VO _{2peak} ; physical component score of SF-36; quality of life index and life satisfaction index; decreased self-reported depression (Beck Depression Index)	Supervised exercise sessions by 2 exercise physiologists	2 participants dropped out (reason not given) and unclear which group; no adverse events
Matsumoto et al, 2007 ¹²⁷	ESRD on hemodialysis (n=55; 22 training, 33 control)	Intervention: 12 months of supervised in-center cycling performed pre-dialysis; started at 2–5 minutes/session until 20 minutes of continuous cycling/session; increased intensity based on RPE with heart rate check targeting 60–70% peak heart rate; Control: usual care (none)	QOL: physical functioning, Role-physical, vitality, mental health of SF-36; muscle mass (creatinine)	Not indicated	Adherence not recorded; 6 patients dropped out (5 in training and 1 in control); no adverse events

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Study	Population	Intervention/control	Results	Monitoring	Adherence/Adverse Events
			generation rate); greater serum albumin		

Abbreviations: ACSM, American College of Sports Medicine; VO2peak, peak oxygen volume; METS, metabolic equivalent scale; BP, blood pressure; DM, diabetes mellitus; RPE, relative perceived exertion; PD, peritoneal dialysis; SF-36, Short Form Health Survey; QOL, quality of life.

Table 3

Exercise recommendations for CKD and ESRD patients

Type	Frequency	Intensity	Time
Aerobic (cycling, walking, swimming)	Wk 1–2: 2x/wk; Wk 3–5: 3x/wk	Wk 1–2: Moderate (RPE 11–13 on scale of 6–20), 55–70% max HR; Wk 3–5: Moderate (RPE 11–16), 55–90 % of max HR	20 min/day (or bouts of 3–5 min of intermittent exercise)
Resistance (multi-joint exercises affecting more than one muscle group and targeting agonist and antagonist muscles)	Wk 1–5: 2x/wk	Wk 1–2: 60–70% of 1-RM; Wk 3–5: 1 RM	Minimum of 1 set of 10–15 repetitions; gradually increase to 2–4 sets; choose 8–10 different exercises to work major muscle groups; rest 2–3min between sets; rest ≥48hrs between sessions
Flexibility (Combine with Aerobic and Resistance when possible)	5x/wk		10 min/day

Exercise recommendations based on Smart et al⁹⁸, Koufaki et al⁹⁹ and Thompson et al¹⁰³. Abbreviations: RPE – Relative Perceived Exertion, RM – repetition maximum, HR – heart rate. Special Considerations: For patients on beta blockers use RPE instead of HR. Patients on vasodilators (e.g. alpha-blockers, CCB) would require extended cool-down period after exercise. Arms with active dialysis access can be exercised during non-dialysis times. PD patients may have more effective exercise with smaller dwell volumes, although fluid in the abdomen is not a contraindication to exercise.

Table 4
Aerobic exercise recommendations for CKD and ESRD Patients based on baseline activity

Baseline Activity*	Frequency	Intensity	Time	Type
Sedentary	3–5/wk	Light-moderate (RPE 3–6 on a scale of 0–10)	20–30min/day	Walking, 3000–3500 steps
Minimal physical activity/no exercise/moderate to highly deconditioned	3–5/wk	Light to moderate (RPE 3–6 on a scale of 0–10)	30–60 min/day	Walking, 3000–4000 steps
Sporadic physical activity/no or suboptimal exercise/moderate to mild deconditioned	3–5/wk	Moderate to hard (RPE 6–8 on a scale of 0–10)	30–90min/day	Walking, >3000–4000 steps; goal >5400–7900 steps and total of ~150min/wk moderate intensity

Note: Baseline activity determined using pedometer¹²⁸. Abbreviations: RPE, relative perceived exertion.