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Exercise in Individuals with CKD

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Abstract

There are few studies evaluating exercise in the nondialysis chronic kidney disease (CKD) population. This review covers the rationale for exercise among patients with CKD not requiring dialysis and the effects of exercise training on physical functioning, progression of kidney disease, and cardiovascular risk factors. In addition, we address the issue of the risk of exercise and make recommendations for implementation of exercise in this population.

Evidence from uncontrolled studies and from small randomized controlled trials shows that exercise training results in improved physical performance and functioning among patients with CKD. In addition, although there are no studies examining cardiovascular outcomes, several studies suggest that cardiovascular risk factors such as hypertension, inflammation, and oxidative stress, may be improved with exercise training in this population. Although the current literature does not allow for definitive conclusions about whether exercise training slows the progression of kidney disease, no study has reported worsening of kidney function as a result of exercise training. In the absence of guidelines specific to the CKD population, recent guidelines developed for older individuals and patients with chronic disease should be applied to the CKD population.

In sum, exercise appears to be safe in this patient population if begun at moderate intensity and increased gradually. Indeed, the evidence suggests that the risk of remaining inactive is higher. Patients should be advised to increase their physical activity when possible and referred to physical therapy or cardiac rehabilitation programs when appropriate.

Although much has been written about exercise tolerance and exercise training among patients on dialysis, individuals with non-dialysis dependent chronic kidney disease (CKD) have been relatively understudied, perhaps because of the heterogeneity of the CKD population. While it is well established that patients on dialysis are limited in their physical functioning (1, 2), the question of whether and to what extent patients with CKD are limited is more difficult to address because the answer may differ depending on stage of disease. Similarly, the heavy toll of cardiovascular disease among patients on dialysis was recognized long before the high risk among CKD patients became obvious. The relative dearth of evaluations of exercise in CKD could also be related to concerns about safety in this population. In addition to the potential cardiovascular risk, there are other possible

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concerns, such as electrolyte abnormalities, hypoglycemia, and exercise-related hypertension to name a few. This review will focus on the available data to address three potential goals of exercise interventions among patients with CKD: improvement in physical functioning, prevention of cardiovascular complications, and slowing of the progression of CKD. A glossary of terminology is provided in Box 1.

Box 1

Exercise terminology

Aerobic training

training that improves the efficiency of the aerobic energy- producing systems and that can improve cardiorespiratory endurance or fitness.

Cardiorespiratory endurance or fitness

A health-related component of physical fitness that relates to the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity.

Endurance training

Repetitive, aerobic use of large muscles (e.g., walking, bicycling, swimming).

Exercise

Planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness. (Often used interchangeably with exercise training.)

Exercise tolerance or exercise capacity

The maximum level of metabolic work achieved during exercise testing.

Flexibility

A health-related component of physical fitness that relates to the range of motion available at a joint.

Functional limitation

A deficit in the ability to perform a discrete task, such as stair climbing.

Maximal oxygen consumption (VO_{2max})

The maximal capacity for oxygen consumption by the body during maximal exertion. Also known as aerobic power, maximal oxygen uptake, and cardiorespiratory endurance capacity.

Metabolic equivalent (MET)

A unit used to estimate the metabolic cost (oxygen consumption) of physical activity. One MET equals the resting metabolic rate of approximately 3.5 mL O_2/kg/min.

Peak oxygen consumption (VO_{2peak})

The peak oxygen consumption by the body achieved during maximal exercise testing. (This term is more general than maximal oxygen consumption [VO_{2max}] and takes into account the possibility that the maximal oxygen consumption might not have been reached.)

Physical activity

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Bodily movement that is produced by the contraction of skeletal muscle that increases energy expenditure above basal levels. *Moderate activity* is the level that causes some increase in breathing or heart rate and is perceived as light to somewhat hard (e.g., brisk walking). *Vigorous activity* is the level that causes a large increase in breathing or heart rate and is perceived as hard or very hard.

Physical fitness

A set of attributes that people have or achieve that relates to the ability to perform physical activity. These include cardiorespiratory fitness, muscle strength, and flexibility.

Physical function or functioning

A fundamental component of health status describing the state of those sensory and motor skills necessary for usual daily activities.

Physical performance

The execution or accomplishment of specific physical tasks (e.g., walking, stair-climbing).

Resistance training

Training designed to increase strength, power, and muscular endurance.

Strength

The ability of the muscle to exert force.

Note: Reproduced from Mitch and Ikizler[52], with permission of Lippincott Williams & Wilkins.

Physical performance and functioning among patients with CKD

Several studies in patients with CKD stages 3 through 5 clearly demonstrate that peak oxygen consumption (VO_{2peak}) is lower compared with population norms or with healthy control groups, averaging 50%–80% of healthy levels (Table 1).[3–10] The range of VO_{2peak} values reported in several CKD cohorts in Table 1 suggests that many patients with CKD are limited in performing activities such as housework and shopping (ie, do not have the exercise capacity to sustain these activities) (refs). Or, another frame of reference: many individuals with CKD would meet Social Security criteria for cardiovascular disability based on their low VO_{2peak}.[11] In addition, a group from Sweden studied other measures of physical performance among 55 patients with an average estimated glomerular filtration rate (eGFR) of 12 mL/min/1.73m^2 for men and 11 mL/min/1.73m^2 for women[12] and found that performance was reduced compared with healthy population norms for all tests, including grip strength (78 ± 25% for men and 84 ± 22% for women), rising from a chair (9% of men and 26% of women unable to rise even once without using the arms), timed “get up and go” test (73% of men and 70% of women needing >10s), and maximum gait speed (80 ±19% for men and 82 ± 18% for women).

Padilla et al showed that physical performance, as measured by peak oxygen consumption, 6-minute walk test, comfortable and maximal gait speed, and sit to stand test, was reduced compared with normative values among 55 patients with eGFR 29.9 ± 17.0 mL/min/ 1.73m^2(13). In addition, self-reported physical functioning based on the Physical Functioning scale and the Physical Component Summary (PCS) measure of the SF-36 were low.

Self-reported function was also measured at baseline in the LORD (Lipid lowering and Onset of Renal Disease) study, which enrolled 120 patients with CKD stage 2–4.[14] Self-reported physical functioning among LORD participants was somewhat lower than population norms but considerably better than that of hemodialysis patients (PCS scores of 46, 50, and 36, respectively).[15] Kusek et al studied self-reported functioning among 1,094 participants in AASK (African American Study of Kidney Disease and Hypertension) with an average eGFR of 45.7 ± 13.0 mL/min/1.73m2.[16] They found that the SF-36 PCS score was lower among these participants (43.4 ± 10.9) than population norms (50 ± 10) and was also lower among those with lower eGFR. In addition, in univariate and multivariable analysis, the PCS score was significantly higher among those who reported that they currently exercise than those who did not exercise. AASK participants reported worse physical functioning than hypertensive African Americans without CKD but better functioning than hemodialysis patients from the HEMO study.

Association of physical function with kidney function

Clyne et al examined exercise capacity in 58 patients with CKD stages 4 and 5 who had a range of glomerular filtration rate (GFR) from 3–32 mL/min, and found that exercise capacity was correlated with GFR after adjustment for age, sex, and hemoglobin concentration.[17], Padilla et al did not find a correlation between peak oxygen consumption and eGFR, although maximal gait speed and PCS score were correlated with eGFR.[13] In another cross-sectional analysis designed to cover a wide range of kidney function, we recently enrolled 57 participants, of whom 19 were without CKD, 22 had CKD (eGFR of 30.7 ± 12.3), and 16 patients were receiving hemodialysis.[18] We found that physical activity was strongly correlated with kidney function. Nevertheless, quadriceps muscle cross-sectional area measured by magnetic resonance imaging, maximal voluntary knee extension, and the Physical Functioning scale score of the SF-36 were correlated with kidney function even after adjusting for physical activity.

In the Heart and Soul study, exercise capacity was impaired in patients with eGFR of 60–90 mL/min (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4 – 3.8 for exercise capacity <5 metabolic equivalent tasks [METs]), although not to the same extent as for patients with eGFR< 60 mL/min (OR, 6.7; 95% CI, 3.8 – 11.8), suggesting that maximal exercise tolerance may become impaired fairly early in the course of CKD. On the other hand, compared with the reference group with eGFR >90 mL/min, the OR for self-reported poor physical function (score <75 on the Seattle Angina Questionnaire (SAQ) 9-item physical limitation scale) was 1.0 (95% CI, 0.7 – 1.5) for eGFR 60–90 mL/min and 2.0 (95% CI, 1.3 – 3.1) for eGFR<60 mL/min, suggesting that self-reported physical functioning may not become impaired until CKD has reached stage 3.

Odden et al also examined the relationship between eGFR, estimated using either cystatin C or creatinine (by the MDRD Study equation) and physical performance among participants in the Health and Body Composition (Health ABC) study.[19] They found that lower eGFR was associated with worse 400-m walk time, lower extremity performance, grip strength, and knee extension strength. Worse kidney function was associated with worse physical performance for eGFR > 60 mL/min/1.73m^2 (as it was for 78.5% of participants) and eGFR <60 mL/min/1.73m^2 and whether kidney function was estimated using creatinine or cystatin C, although the associations were stronger for cystatin C-based estimates.

We are aware of only one longitudinal study that assessed the extent to which physical functioning deteriorates as kidney function declines. Leikis et al studied peak oxygen consumption during bicycle ergometry, isometric knee extension maximum voluntary contraction (MVC), isokinetic knee extension, and thigh muscle cross-sectional area by computed tomography among 12 patients with CKD, nine of whom had follow-up testing over a period of up to two years.[7] Creatinine clearance declined from 35 ± 13 to 25 ± 11 ($p<0.007$) without a substantial decline in hemoglobin (from 13.1 ± 10 g/dL to 12.6 ± 1.1 g/dL, $P = 0.26$). VO_{2peak} declined by 9% ($P = 0.03$) and knee strength by approximately 10% depending on the speed ($P=0.04$), but no change in thigh muscle cross-sectional area or knee extension MVC was detected. The authors concluded that physical performance decreases as kidney function declines in a manner that is not related to anemia.

Taken together, the available evidence suggests that at least some aspects of physical functioning are impaired even in early stages of CKD. However, the extent to which these impairments among patients with CKD are independent of age, comorbidity and physical inactivity is unclear. These factors may also mediate physical dysfunction among patients with more advanced stages of CKD, but limited data suggest that there is CKD-related dysfunction that is independent of age and inactivity. There has been almost no exploration of the potential causes or mechanisms of poor physical functioning among patients with CKD. Uremic toxins, vitamin D deficiency, hyperparathyroidism, metabolic acidosis, and anemia are among the possibilities; any or all of these could act to cause muscle wasting and/or altered neuromuscular function.

Exercise Training in CKD

Effect of exercise training on physical functioning and performance

There is significant evidence to suggest that exercise training improves physical functioning in patients receiving dialysis, including at least 9 uncontrolled (time series) trials, 7 nonrandomized but controlled trials, and 13 randomized controlled trials.[20] All but 2 of these 29 trials reported improvements in VO_{2peak}, with average increases between 17%-23%, as well as in physical performance measures (gait speed, 6-minute walk and sit-to-stand test) and self-reported physical functioning (SF-36 Physical Functioning and PCS scores).[1,2,20,21]

There is much less evidence as to the effects of exercise training in patients with CKD. We found 12 publications from 10 studies that reported the results of exercise training in patients with CKD (Table 2). There were seven studies of aerobic exercise training, one of resistance training, and 2 that incorporated both aerobic and resistance exercise. Six were randomized controlled trials, one was a crossover design, and 3 were quasi-experimental controlled studies. The duration of exercise also varied widely from 12 weeks to 20 months, but most programs lasted for 3–12 months. Exercise was supervised in all studies, but 2 studies also included unsupervised home exercise.[8,9] Leehy et al added home exercise as a continuation of a program that was initially begun as a supervised intervention,[8] and Mustata et al included home walking 3 times per week concurrently with supervised treadmill walking twice per week.[9] The studies were small, ranging from 7 to 17 subjects in the exercise intervention group.

Seven studies reported improvements in VO_{2peak} or maximal work-rate achieved (cycling) or treadmill walking time.[3,4,6,8–10,22] The magnitude of change in exercise capacity was similar to that reported in patients receiving dialysis. One study reported improved 6 minute walk distance and functional mobility as measured by the get up and go test,[23] and one study reported clinically meaningful improvement in overall quality of life (the EQ-5D index) in the exercise group, and in the Role-Physical domain of the SF-36.[9] Four studies reported increased muscle strength.[5,10,22–24] In addition to increased muscle strength, resistance exercise was shown to result in increases in type I and type II muscle fiber size,[5,24] increased mitochondrial DNA,25 and increased leucine oxidation and increased prealbumin,[5] all signs of an anabolic effect. However, Gregory et al reported no change in insulin like growth factor 1 (IGF-1), IGF-2, or IGF binding proteins with aerobic exercise training despite an improvement in exercise capacity.[10]

Effect of exercise training on potential mediators of cardiovascular risk

There is now an extensive literature demonstrating that cardiovascular disease is not only the number one cause of mortality among patients receiving dialysis[26] but is also a major source of morbidity and mortality among patients with CKD.[27–31] Many potential mediators of this increased risk have been proposed, including an increased prevalence of traditional risk factors, such as hypertension, hyperlipidemia, and diabetes, as well as other factors that may relate more directly to reduced kidney function, such as endothelial dysfunction, increased sympathetic activity, oxidative stress,[32] inflammation, and abnormal lipid patterns.[33,34] Several of these candidate mediators are potentially ameliorated by exercise interventions. No studies of exercise in patients with CKD have examined cardiovascular outcomes, but a few studies have examined the effects of exercise on potential mediators of cardiovascular risk.

Mustata et al performed a randomized controlled trial of the effects of one year of combined supervised and home-based exercise on arterial stiffness among 20 medically stable sedentary patients with stage 3 or 4 CKD.[9] Arterial stiffness was estimated by the augmentation index, derived from pulse wave analysis of the radial artery.[35] Supervised training consisted of twice-weekly in-center sessions with the choice of treadmill, stationary cycle, or elliptical trainer at a target intensity of 40%–60% of VO_{2peak} for 5–20 minutes. Exercise duration was increased by 5%–10% each week to a maximum of 60 minutes. Home training, initiated in the second month, consisted of walking 3 days per week. Overall, the achieved exercise fell short of targets, with subjects achieving a median total weekly exercise time of 43 minutes. Despite the less-than-intended duration of exercise, those assigned to the exercise group had significantly lower augmentation index after 12 months (−11.7%; 95% CI, −18.8 to −4.6%; $P = 0.003$).

Castaneda et al performed a randomized study of 12 weeks of resistance exercise training 3 times per week among 26 patients with CKD on a low protein diet (0.6 g/kg/d). In addition to examining outcomes related to muscle size and strength,[5] they measured CRP (C-reactive protein) and IL-6 (interleukin 6) levels before and after the intervention and found that both were reduced after the intervention (CRP, −1.7 mg/L in the exercise group vs. +1.5 mg/L in the control group [P=0.05; IL-6, −4.2 pg/mL in the exercise group vs. +2.3 pg/mL in the control group [P=0.01]).[24]

In a 12-week study of a water-based exercise intervention in which 17 patients exercised, Pechter et al reported a reduction in blood pressure and oxidative stress, indicated by a decrease in products of lipid peroxidation and increase in reduced glutathione.[36] Boyce et al also reported significant reductions in blood pressure with exercise training and a return back to baseline levels with a period of detraining.[4]

Effect of exercise training on progression of CKD

Exercise has been shown to lead to less proteinuria and a lower index of glomerular sclerosis in rats after 5/6 nephrectomy.[37,38] There have only been a few small studies that have investigated the effects of exercise on progression of CKD in humans. Eidemark et al randomly assigned 30 nondiabetic patients with CKD (median GFR, 25; range, 10–43 mL/min/1.73m^2) to either exercise training or control groups.[3] The exercise group did mainly bicycle ergometer exercise at home, with some running and swimming, which was gradually increased to approximately 60%–75% of the maximal exercise capacity for approximately 30 minutes per day. After an average of 18 months, the exercise group increased their

VO_{2peak}, but there was no change in blood pressure or rate of loss of GFR (monthly change of −0.27 [95% CI, 0.57 to −1.31] mL/min in the exercise group vs. −0.28 [95% CI, 0.18 to −0.93] mL/min in the control group). Although it is unclear whether this study had adequate power to detect a difference in rate of progression of CKD, the authors conclude that any such effect would be too small to be of any clinical interest. Leehy et al reported that 18 months of aerobic exercise training did not significantly alter VO_{2peak}, GFR, hemoglobin, serum lipids, or CRP, but power was limited because only 7 patients in the exercise group and 4 patients in the control group finished the study.[8] In a third small study, Toyama et al nonrandomly assigned 10 patients with CKD to exercise for 12 weeks and 9 patients to a nonexercising control group.[39] The anaerobic metabolic threshold, high-density lipoprotein cholesterol, and eGFR were increased in the exercise group, and the change in eGFR correlated with the change in anaerobic metabolic threshold and high-density lipoprotein cholesterol. The nonrandomized study of Pechter et al reported significant reduction in proteinuria, and cystatin C and "ameliorating trends" in GFR.[36] Although not discussed by Casteneda, the GFR increased in the resistance training group compared with the control (GFR change +1.18 vs −1.62; p=0.048).[5] GFR changes were not observed (either deterioration or improvements) in any other studies of aerobic exercise.

Overall, no interventional study has examined the effects of exercise training on change in kidney function among patients with CKD with sufficient rigor and power to be conclusive. On the other hand, no study to date has shown a detrimental effect of exercise on progression of kidney disease.

Safety of exercise among patients with CKD

There have been no reported cardiac events in any of the published exercise training studies in hemodialysis patients. Symptom-limited exercise testing was performed in 2 studies of patients with CKD (Table 1). Leehey reported that 2 of 19 subjects tested had positive stress tests,[8] and Padilla et al reported that 8 of 32 (25%) patients tested exhibited abnormal response to exercise, with 3 having S-T segment depression, 2 with hypertensive responses (systolic blood pressure reaching 260 mmHg) and 1 with a hypotensive response (>20 mm Hg drop in systolic blood pressure), and 2 patients exhibiting significant ventricular ectopy. All the abnormal exercise responses occurred in patients with known cardiac disease, and 3 also had diabetes. None was associated with adverse outcome. Beyond these studies, the risks associated with exercise in the CKD population have not been studied. A few epidemiologic studies in patients with end-stage renal disease suggest that low physical activity and/or low self-reported physical functioning are associated with poor outcomes,[40,41] but we are aware of no data specific to CKD, leaving the nephrology community to put the risks of exercise and physical inactivity into perspective based on what is known in other populations.

Regular physical activity is widely recommended for the general population and for patients with documented cardiac disease or at high risk.[42–44] These recommendations are based on substantial epidemiological, clinical and basic science evidence of prevention or delay in developing coronary artery disease in the general population. There is, however, an acute and transiently increased risk of acute myocardial infarction and sudden cardiac death in susceptible individuals during vigorous exercise. The American Heart Association Council on Nutrition, Physical Activity and Metabolism and the Council on Clinical Cardiology in collaboration with the American College of Sports Medicine[45] and the 2008 Physical Activity Guidelines for Americans from the Department of Health and Human Services[43] have similar statements regarding the risks of exercise. While engaged in vigorous physical activity, all individuals, even those who are regularly active, have greater risk of sudden adverse cardiac events than when they are less active. Even so, compared with inactive individuals, active people have lower risk both during activity and inactivity. There is greater risk of adverse cardiac events for those who persist with a sedentary lifestyle than those who gradually increase their regular levels of physical activity.[45] In comparison with risks associated with vigorous activities, risks of sudden cardiac adverse events during light and moderate intensity activities are lower.

Although asymptomatic individuals are encouraged to consult a health care provider before increasing their level of physical activity, to date there are no data from controlled trials that are helpful in guiding the use of exercise testing in asymptomatic adults without known or suspected coronary artery disease before they start an exercise training program.[45] The American College of Cardiology/American Heart Association Guidelines on Exercise Testing[46] and the American College of Sports Medicine[47] have offered some recommendations, mainly that individuals who appear to be a greater risk of having underlying coronary artery disease should be considered for exercise testing before beginning a vigorous (> 6 METs or > 60% of peak heart rate) exercise training program. Both groups advise exercise testing prior to exercise training for patients with diabetes mellitus or known cardiovascular disease.

These guidelines all refer to participation in a vigorous exercise training program. Of note, there is no mention of exercise testing before becoming physically active in the American Heart Association/American College of Sports Medicine Recommendations for Physical Activity and Public Health in Older Adults, probably because the recommendations are for low intensity (light to moderate) activity that is gradually increased, and because recommendations are for participation according to their abilities for individuals with chronic conditions.[48] Thus exercise according to these recommendations places individuals at less cardiovascular risk than vigorous exercise. Since a requirement for exercise testing before starting a program of low intensity physical activity would constitute a substantial barrier to participation for many, such a requirement could contribute to the increased risk associated with remaining sedentary. Furthermore, exercise testing typically is a symptom-limited or near maximal effort. Thus the risks of exercise testing are greater than those of exercise training and of increasing participation in moderate activity. For these reasons, testing before initiation of exercise remains controversial, even in high risk populations such as individuals with CKD.

Risk assessment and preparticipation screening should be done on an individual basis among patients with CKD as they are likely to be at higher risk of exercise-induced death than the general population but also stand to benefit more from increasing activity. Hypertension should be controlled before exercise, and the American College of Sports Medicine recommends not exercising if resting systolic blood pressure exceeds 200 mmHg and/or diastolic blood pressure exceeds 110 mmHg.[47] Risk will be reduced with appropriate education of the patients about abnormal responses and symptoms and when to reduce intensity of exercise, defer exercise on a given day, stop exercise and contact the physician; prudent recommendations for starting and progressing with the program; and regular assessment of participation and responses to their program. Risk will be increased if patients remain sedentary.

Recommendations

The optimal recommendations for exercise for patients with CKD have not been determined. However, it is reasonable to follow recommendations published by the AHA for older adults,[48] which are also explicitly intended to be relevant to younger individuals with clinically significant chronic conditions and/or functional limitations, a description that applies to most patients with CKD. It is also reasonable to refer patients with known cardiac disease to cardiac rehabilitation. Kutner et al[49] used Medicare expenditure data and found low levels of referral to cardiac rehabilitation in hemodialysis patients following coronary artery bypass surgery despite clear benefit to patients and cost effectiveness.

For those who do not qualify for cardiac rehabilitation, the recommendations for older adults are: *"To promote and maintain health, older adults need moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week or vigorous intensity aerobic activity for a minimum of 20 minutes on three days each week."* Moderate and vigorous activity is clarified as a level of effort relative to an individual's aerobic fitness. *"Given the heterogeneity of fitness levels in older adults, for some a moderate intensity is a slow walk, and for others, it is a brisk walk."* These recommendations also include muscle strengthening, flexibility and balance exercise, also tailored to an individual's relative intensity and progressed gradually (Table 3).

Resources that are appropriate for patients with CKD and provide direction and step by step instructions for these components of fitness are available in free download format from the Life Options website[50] in the form of "Exercise for the Dialysis Patient" or from the National Institute on Aging in a pamphlet entitled, "Exercise & Physical Activity".[51]

Although assessment and recommendations for physical activity are not currently a standard part of the care of individuals with CKD, the evidence suggests that they should be. At the very least, recognizing that nephrologists may not have the time, training or inclination to learn to give a full exercise prescription, the following can be done within clinical visits with patients. 1) Ask about physical activity participation and help identify barriers; 2) Recommend increasing activity if levels are low by recommending walking whenever feasible (unless the patient is nonambulatory or has gait instability or other contraindications to exercise (ie, unstable angina, uncontrolled heart failure, uncontrolled hypertension); 3) Provide educational materials[50,51]; 4) Refer to a trained health care professional who is qualified to work with patients with chronic disease, such as physical/occupational therapists, cardiac rehabilitation specialists, or clinical exercise physiologists. These referrals should then be regularly followed up during the routine clinic visits to assess participation, progress and provide encouragement because patients are more likely to change their behavior if they perceive that their doctors support their progress. Finally, despite the cost and difficulty of conducting rigorous studies of exercise and physical activity among patients with CKD, larger studies of strategies to increase and maintain greater levels of activity are urgently needed in this population so that recommendations can be based on direct evidence rather than extrapolated from the general or older population.

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Table 1

Exercise Capacity Among Patients With CKD Compared With Healthy Controls or Norms

Study	No.	Age	(e)GFR	VO_2	Fraction of reference VO_2 (%)[‡a]
Eidemak et al (3), 1997	15 (8M, 7F)	45	26	25 mL/kg/min	62%
Boyce et al (4), 1997	8	50.4 ± 6.8		1.3 L/min	66%
Castaneda et al (5), 2001	14 (8M, 6F)	65 ± 9	24.8	16.0 ± 5.1 mL/kg/min	59%
Pechter, 2003 (36)	17 (7 M, 10 F)	52	62.9 ± 5.9	18.8 ± 0.9 mL/kg/min	63%
Leikis, 2006 (7)	12 (10 M, 2 F)	49 ± 11	31 ± 13	22.2 ± 4.0 mL/kg/min	82 ± 13%
Leehey, 2009 (8)	7 (7 M)[*]	66	44 ± 36	14.9 ± 1.1 mL/kg/min	45%
Mustata, 2010 (9)	10 (6 M, 4 F)[†]	64	27	15.8 mL/kg/min	60%
Gregory, 2011 (10)	10	57.5 ± 11.5	30 ± 18	17.3 ± 5.2 mL/kg/min	52%

Note: Values shown are reported in the studies cited or estimated from the Guidelines for Exercise Testing and Presciption from the American College of Sports Medicine.[47]

[*] All patients had diabetes mellitus.

[†] Patients with diabetes mellitus excluded.

[**] Workload by bicycle ergometry.

[a] Reference VO_2 is VO_2 level in the healthy population.

Abbreviations: CKD, chronic kidney disease; (e)GFR: (estimated) glomerular filtration rate, VO_2: oxygen consumption per unit time.

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Table 2

Summary of Exercise Training Studies in Patients With CKD Not Requiring Dialysis

Study	No. (exercise vs control)	Age(y)	Kidney Function	Design	Training	Outcomes in exercise group
Clyne[22]	10 vs 9	47 ± 8	15 ±7 mL/min/1.73 m^2	RCT		Increase in: max work rate, muscle strength
Eidemak[3]	15 vs 15	44.5	25 (range, 10–43) mL/min/ 1.73m^2	RCT	20 mo, 30 min cycling & other activities	Increase in max work capacity No change in GFR
Boyce[4]	8 vs 0	50.4 ± 6.8		Single-subject reversal	4 mo, 3×/wk, walking & cycling <=60 min at 70% HR	Increase in: VO_{2peak}, vent threshold Decrease in: SBP, DBP
Heiwe[23]	16 vs 9 (older age)	74 ±6	17 ± 5 mL/min	Quasi- experimental controlled	12 wk, 3×/wk, strength training (20 reps/leg at 60% of 1RM) & 30 min low- intensity exercise	Increase in: 1RM, 6 min walk distance, "get up and go" functional mobility, dynamic & static strength No change in sickness impact on profile
Pechter[36]	17 vs 9	50	66.8 ± 9.1 mL/min	Quasi- experimental controlled	12 wk, 2×/wk, low-intensity water exercise for 30 min/ session	Increase in: VO_{2peak}, peak work rate, glutathione Decrease in: lipid peroxidase, proteinuria
Leehey[8]	7 vs 4 (diabetic, obese)	66	44 ± 36 mL/min/1.73m^2	RCT (pilot study)	24 wk (3×/wk for 6 wk & home exercise for 18 wk), 40 min/ session at 45–85% VO_{2peak}	Increase in treadmill time No change in proteinuria
Mustata[9]	8 vs 10	68	27.5 mL/min/1.73m^2	RCT (pilot study)	12 mo, 2×/wk supervised (treadmill, cycling) & 3×/wk home walking, <= 60 min at 60% VO_{2peak}	Increase in: VO_{2peak}, treadmill walking time, arterial augmentation index Clinically meaningful increase in HRQoL
Casteneda[5,24]; Balakrishnan[25]	14 vs 12	65±10	29.5 ± 27.4 mL/min/1.73 m^2	RCT	12 wk, 3×/wk, 80% of 1RM	Increase in: muscle strength, type I & type II muscle fiber size, mDNA, leucine oxidation, serum prealbumin Decrease in: CRP, IL-6
Toyama[39]	10 vs 9	71.7 ± 11	47.5±11.6	Quasi- experimental controlled	12 wk, 1×/wk supervised 30 min cycling & 30 min home walking	Increase in: ventilatory threshold, LDL cholesterol, eGFR Decrease in triglycerides
Gregory[10]	10 vs 11	55.0±11.1	0.65 ±0.35 mL/s/1.73 m^2	RCT	48 wk, 3×/wk, aerobic exercise, 55 min/session at 50%-60% VO_{2peak}; also, starting at 24 wk, 2×/wk resistance exercise (1–2 sets of 15 reps major muscle groups)	Increase in: VO_{2peak}, treadmill time, leg strength No change in IGF-1, IGF-2, IGFBP-1, IGFBP-2

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Abbreviations: IGF-1: insulin like growth factor 1, IGF-2: insulin like growth factor 2, IGFBP-1, insulin-like growth factor binding protein 1; IGFBP-2; insulin-like growth factor binding protein 2; $VO_{2:peak}$, peak oxygen consumption; eGFR: estimated glomerular filtration rate, 1RM, 1-repetition maximum (maximum amount of weight that can be lifted in a single repetition): RCT: randomized controlled trial, CRP: C-reactive protein, IL-6, interleukin 6; GFR: glomerular filtration rate; max, maximum; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HRQoL, health-related quality of life; mDNA, mitochondrial DNA; LDL, low-density lipoprotein; CKD, chronic kidney disease.

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Table 3

Exercise Recommendations for Older Adults or Younger Individuals With Clinically Significant Chronic Conditions and/or Functional Limitations

Type of physical activity	Duration and Frequency	Special considerations
Aerobic activity (one of the following)		
Moderate intensity (5–6 on a 10-point scale)[*†]	>=30 minutes on most if not all days of the week	To reach 30 min/d, bouts of >= 10 min are recommended; minimum of 5 d/wk
Vigorous intensity (7–8 on a 10-point scale)[*]	20 min per session, >=3 d/wk	--
Muscle-strengthening activity	>=2 (nonconsecutive) d/wk	8–10 exercises involving major muscle groups; 10–15 repetitions per exercise
Flexibility	>=2 d/wk; >=10 min/d	For those at risk for falls, include exercises to maintain or improve balance

Notes: Based on Nelson et al.[48]

[*]Intensity should be relative the individual's level of fitness and ability rather than to an absolute scale.

[†]Walking is preferred for ambulatory patients, and supervision is not necessary to achieve benefit.