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Renal rehabilitation in patients with chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is a worldwide public health problem. Physical activity and exercise endurance are low in patients with CKD, and a sedentary lifestyle contributes to increased morbidity and mortality risk. However, there are a few studies evaluating regular exercise in non-dialysis CKD patients. This review focuses on the importance and benefits of regular exercise in non-dialysis CKD patients. Systematic reviews and meta-analyses of randomized controlled trials reported that exercise-based renal rehabilitation improved aerobic capacity, muscular functioning, cardiovascular function, walking capacity, and quality of life in dialysis patients. However, few studies indicated that regular exercise or exercise therapy could improve not only physical function but also renal function and lower risk of overall mortality and renal replacement therapy in non-dialysis CKD patients. Animal studies have demonstrated that chronic exercise has renoprotective effects in several CKD models. Exercise therapy could be an effective clinical strategy for improving renal function, lowering the risk for renal replacement therapy and cardiovascular disease in non-dialysis CKD patients.

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. For example, more than 320,000 patients undergo hemodialysis (HD) in Japan, which corresponds to every 1 in 400 people. Furthermore, the numbers of patients with CKD in Japan is more than 13% of the total population. Cardiovascular disease (CVD) remains a major cause of hospitalization and mortality in CKD patients across all stages, and CKD is one of the most potent known risk factors for CVD [1]. CKD patients with HD have a high rate of mortality with CVD, such as chronic heart failure, and a higher mortality risk has been reported for sedentary HD patients [2]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend moderate intensity aerobic exercise most days of the week for the prevention of CVD in dialysis patients [3]. However, guidelines pertaining to the earlier stages of CKD remain to be developed and integrated into clinical practice. The lack of established guidelines pertaining to regular exercise for the prevention of CVD in these early stages of CKD is noteworthy, because these individuals are more likely to die from CVD than progress to renal failure [1]. Thus, this review focuses on the importance and benefits of regular exercise or exercise therapy in non-dialysis CKD patients as renal rehabilitation [4].

Physical capacity in CKD patients

Physical inactivity is well-recognized as a major health issue today. Regular exercise is important in maintaining health and preventing chronic disease, and is increasingly accepted as a valuable therapeutic intervention in many long-term conditions.

Exercise endurance is lowered in CKD patients, and this phenomenon becomes more distinct as renal dysfunction advances. Aerobic capacity is impaired ranging from 50 – 80% of normative values in the early stages of CKD (Stages 1–4) [5]. Impaired physical function has also been reported in these earlier stages of CKD [6] with declines in self-reported function becoming apparent around Stage 3 [7]. When patients reach Stage 5 CKD and commence renal replacement therapy (RRT), physical activity levels are approximately 25% of those recorded in age-matched sedentary healthy individuals [8]. CKD is also associated with a higher prevalence of disability, and difficulty with activities of daily living (ADL) was reported by 17.6%, 24.7%, and 23.9% of older (65 years) and 6.8%, 11.9%, and 11.0% of younger (20-64 years) adults with no CKD, stages 1 and 2, and stages 3 and 4, respectively [9].

The mechanisms responsible for the impaired physical capacity in CKD patients are not fully elucidated. While factors such as anemia [7] and inflammation [10] may play a role, the impaired physical function including 400-m walk time, lower-extremity performance, grip strength and knee extension strength was associated with declining glomerular filtration rate (GFR) independently of age, anemia and comorbidity [11]. The relationship between renal function and physical function is thought to be mediated through muscle strength in mild to moderate CKD [11]. Additionally, lower extremity physical performance including gait speed, timed up and go, 6-min walk is substantially impaired in non-dialysis CKD patients and is associated with all-cause mortality after adjustment [12]. Associations with mortality were similar in magnitude to renal function and were stronger than traditionally measured biomarkers of CKD. The impaired physical capacity leads to reduce the quality of life (QOL) and further aggravated by a sedentary lifestyle. As well as being a strong cardiovascular risk factor, physical inactivity is associated with an increased risk of rapid GFR decline in CKD patients [5,13].

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Effects of regular exercise in non-dialysis CKD patients

Systematic reviews and meta-analysis of randomized controlled trials reported the effects of regular exercise for at least 8 weeks in stages 2–5 of CKD, HD patients, or kidney transplant recipients [5,14]. Forty-one trials (928 participants) that compared exercise training with sham exercise or no exercise were included. Overall, improved aerobic capacity, muscular functioning, cardiovascular function, walking capacity, and health-related QOL were associated with various exercise interventions. Significant increases in muscular strength have been reported throughout all stages of CKD following aerobic exercise, but more so following resistance exercise training. These increases in aerobic capacity and muscular strength have been observed following as little as three months of exercise training carried out at least 3 times per week. Notably, the preponderance of the data collected in these studies was of HD patients and aerobic exercise program participants [14].

There have been few studies that have investigated the effects of exercise on progression of CKD in humans. Castaneda et al. [15] performed a randomized study of 12 weeks of resistance exercise training 3 times per week in 26 patients on a low-protein diet (0.6 g/kg/day) and reported that GFR increased in the resistance training group compared with the control. Pechter et al. [16] performed a nonrandomized study of 12 weeks of a water-based exercise intervention in 17 patients and reported a significant decrease in proteinuria and cystatin C level and ameliorating trends in estimated GFR (eGFR).

Baria et al. [17] randomly assigned 27 patients (eGFR 27.5 ± 11.6 mL/min) were randomly assigned to a center-based exercise group, home-based exercise group or control group, with aerobic exercise being prescribed based upon ventilatory threshold and performed three times per week for 12 weeks. Mean blood pressure decreased in both exercise groups (center-based: 13%, home-based: 10%) and eGFR increased by 3.6 ± 4.6 mL/min in the center-based group. These parameters remained unchanged in the control group.

Greenwood et al. [18] reported single-blind, randomized, controlled, study which examined the effect of moderate-intensity exercise training on kidney function and indexes of cardiovascular risk in non-dialysis patients with progressive CKD stages 3–4. A significant mean difference in rate of change in eGFR was observed between the rehabilitation and usual care groups, with the rehabilitation group demonstrating a slower decline. These results suggested that exercise therapy could be an effective clinical strategy for improving renal function in non-dialysis CKD patients.

Chen et al. [19] reported an association of walking with overall mortality and RRT, such as HD or renal transplant in patients with CKD stages 3–5 [19]. A total of 6363 patients during a median of 1.3 years of follow-up were analyzed. There were 1341 (21.1%) patients who reported walking as their most common form of exercise. The incidence density rate of overall mortality was 2.7 per 100 person-years for walking patients and 5.4 for non-walking patients. The incidence density rate of RRT was 22 per 100 person-years for walking patients and 32.9 for non-walking patients. Walking, independent of patients' age, renal function, and comorbidity were linked to lower overall mortality and lower RRT risk in the multivariate competing-risks regression. The adjusted sub-distribution hazard ratio of walking was 0.67 (95% confidence interval [95% CI]: 0.53–0.84; P<0.001) for overall mortality and 0.79 (95% CI: 0.73–0.85; P<0.001) for the risk of RRT. The SHRs of overall mortality were 0.83, 0.72, 0.42, and 0.41 for patients walking 1–2, 3–4, 5–6, and 7 times per week, respectively, and the SHRs of RRT were 0.81, 0.73, 0.57, and 0.56, for patients walking 1–2, 3–4, 5–6, and 7 times per week, respectively. Walking is the most popular form of exercise in patients with CKD and is associated with a lower risk of overall mortality and RRT. The benefit of walking is independent of patients' age, renal function, and comorbidity.

Exercise-based cardiac rehabilitation for CVD also improved renal function in CVD patients with CKD. Toyama et al. [20] reported that cardiac rehabilitation for 12 weeks significantly improved the anaerobic metabolic threshold, high-density lipoprotein cholesterol (HDL-C) levels, and eGFR. Changes in eGFR correlated significantly and positively with changes in anaerobic metabolic threshold and HDL-C. Exercise therapy correlated with improving renal function in CVD patients with CKD by modifying lipid metabolism. Similarly, Takaya et al. [21] reported that active participation in cardiac rehabilitation was associated not only with improved peak VO_2, but also with brain natriuretic peptide and eGFR in acute myocardial infarction patients with CKD.

Effects of exercise training in CKD model rats

It is necessary to consider the influence of exercise on renal functions because acute exercise causes proteinuria and subsequent reductions in both renal blood flow and GFR. It has also been demonstrated clinically that acute exercise decreases renal function. There are few reports for effects of chronic exercise on renal function in several animal models [22-27]. The results of the animal studies also indicate that regular exercise or exercise therapy may have renal protective effects in non-dialysis CKD patients.

First, the renal effects of moderate chronic exercise and antihypertensive therapy on renal function were assessed in a remnant kidney model of spontaneously hypertensive rats (SHR) with 5/6 nephrectomy and assessed the effects of exercise and antihypertensive therapy [22]. Chronic exercise with treadmill running (20 m/min, 60 min/day, 5 days/week) for 4 weeks significantly attenuated the progression of proteinuria and glomerular sclerosis. Both the angiotensin converting enzyme inhibitor, enalapril (ENA) and the angiotensin II type 1 receptor blocker, losartan (LOS) with exercise significantly decreased blood pressure, and further attenuated the glomerular sclerosis. Exercise, antihypertensive drug, and mean systolic blood pressure remained as significant predictors of proteinuria. These results suggest that exercise does not worsen renal function and has renoprotective effects. Moreover, in this model, antihypertensive therapy has additional renoprotective effects with exercise [22].

Second, we assessed the renal and peripheral effects of moderate to intense chronic exercise (20 and 28 m/min, 60 min/day, 5 days/week) for 12 weeks as well as the effects of the combination of chronic exercise and ENA in 5/6-nephrectomized Wistar-Kyoto rats [23]. Both chronic exercise and ENA blocked the development of hypertension, blunted increases in proteinuria, reduced serum creatinine and blood urea nitrogen, and improved glomerular sclerosis and interstitial fibrosis. Moreover, glomerular sclerosis and interstitial fibrosis in the moderate chronic exercise+ENA group were the lowest among all other nephrectomized groups. Furthermore, chronic exercise enhanced the capillarization and increased the proportion of type-I fibers in the soleus muscle. These results suggest that chronic exercise and ENA have renoprotective effects. These findings also suggest that chronic exercise+ENA provided greater renoprotective effects than did ENA alone, and that moderate +ENA exhibited some additional peripheral effects without any complications [23].

Third, renal and peripheral effects of chronic moderate exercise for 12 weeks were assessed in a rat model of diabetic nephropathy (Goto–Kakizaki rats) and the benefits of combined exercise and LOS [24]. LOS and chronic exercise+LOS significantly decreased systolic blood pressure (SBP). chronic exercise, chronic exercise+LOS, and LOS blunted the increases in proteinuria. The glomerular sclerosis and interstitial fibrosis were significantly improved in the chronic exercise, chronic exercise+LOS, and LOS groups. The glomerular sclerosis, expressions of ED-1 and a-smooth muscle actin in the glomerulus was the lowest, and the number of Wilms' tumor was the highest in the chronic exercise+LOS group. Exercise endurance, the proportion of type I fibers, and capillarization in the extensor digitorum longus muscle were greater in the exercise groups. These results suggest that both chronic exercise and LOS have renoprotective effects, and that chronic exercise+LOS provided greater renoprotective effects than did LOS alone. Further, both chronic exercise and LOS may affect macrophage infiltration, mesangial activation, and podocyte loss in this model of diabetic nephropathy. These results also suggested that exercise has a specific renoprotective effect that is not related to SBP reduction, and can enhance exercise endurance without any renal complications [24].

Finally, effects of chronic exercise on the early stage of diabetic nephropathy were evaluated by focusing on nitric oxide synthase (NOS), oxidative stress, and glycation in the kidneys of Zucker diabetic fatty (ZDF) rats [25]. Male ZDF rats underwent forced treadmill exercise for 8 weeks (Ex-ZDF). Sedentary ZDF (Sed-ZDF) and Zucker lean (Sed-ZL) rats served as controls. Chronic exercise attenuated hyperglycemia with increased insulin secretion, reduced albumin excretion, and normalized creatinine clearance in ZDF rats. Endothelial (e) and neuronal (n) NOS expression in the kidneys of Sed-ZDF rats were lower compared with Sed-ZL rats, while both eNOS and nNOS expression were upregulated by exercise. Furthermore, chronic exercise decreased NADPH oxidase activity, p47phox expression and α-oxoaldehyde levels (the precursors for advanced glycation end products) in the kidneys of ZDF rats. Additionally, morphometric evidence indicated that renal damage was reduced in response to exercise. These data suggest that the upregulation of NOS expression, suppression of oxidative stress and glycation stress in the kidneys may, at least in part, contribute to renoprotective effects of exercise training in the early progression of diabetic nephropathy in ZDF rats [25].

Renal rehabilitation

Urgent efforts should be made to increase the implementation rate of rehabilitation for CKD patients. "The Japanese Association of Renal Rehabilitation" was established in 2011 to evaluate and promote "renal rehabilitation" [4]. Renal rehabilitation was defined as "coordinated, multifaceted interventions designed to optimize a renal patient's physical, psychological, and social functioning, in addition to stabilizing, slowing, or even reversing the progression of renal deterioration, thereby reducing morbidity and mortality. Renal rehabilitation includes five major components: exercise training, diet, and fluid management, medication and medical surveillance, education, psychological and vocational counseling" [4]. Exercise therapy can be an effective clinical strategy for improving renal function and lower RRT risk in non- non-dialysis CKD patients.

Summary

This review focuses on the importance and efficacy of renal rehabilitation for CKD patients. Renal rehabilitation can improve not only the QOL, but also the biological lifespan of CKD patients. Renal rehabilitation is a feasible, effective, and safe secondary prevention strategy following CKD, and offers a promising model for the new field of rehabilitation. Future randomized controlled trials should focus more on the effects of exercise training and rehabilitation programs as these subjects and exercise types have not been studied as much as cardiovascular exercise.

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