Cardiovascular Innovations and Applications

Vol. 2 No. 3 (2017) 387–393
ISSN 2009-8618
DOI 10.15212/CVIA.2017.0006

REVIEW

Chronic Kidney Disease is a New Target of Cardiac Rehabilitation

Masahiro Kohzuki[1] and Osamu Ito[1]

[1]*Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Japan*

Received: 16 June 2016; Revised: 15 March 2017; Accepted: 5 April 2017

Abstract

Chronic heart failure is increasingly prevalent worldwide and is associated with significant morbidity and mortality. The Cochrane review demonstrated that cardiac rehabilitation (CR) resulted in improvements in QOL and a reduction in long-term mortality. Chronic kidney disease (CKD) is another worldwide public health problem. This review focuses on the importance and efficacy of rehabilitation for CKD patients as a new target of CR. Patients with CKD on hemodialysis (HD) have a high mortality rate, with cardiovascular diseases, such as chronic heart failure. A new systematic review and meta-analysis of randomized controlled trials reported that exercise-based renal rehabilitation improved aerobic capacity, muscular functioning, cardiovascular function, walking capacity, and QOL in CKD patients with HD. Moreover, exercise training may have renal protective effects, not only in some animal models of pre-HD CKD, but also in pre-HD CKD patients. Exercise therapy could be an effective clinical strategy in improving renal function, lowering the need for renal replacement therapy, such as HD, and reducing renal transplant risk in pre-HD CKD patients. This led the Ministry of Health, Labor and Welfare of Japan to extend renal rehabilitation partial coverage to stage 4 pre-HD CKD patients for the first time in the world in 2016.

Keywords: chronic kidney disease; rehabilitation; exercise; cardio-renal syndrome; renal protection

Introduction

Chronic heart failure, the common final stage of all heart diseases, is increasingly prevalent worldwide and is associated with significant morbidity and mortality. The Cochrane review demonstrated that exercise-based cardiac rehabilitation (CR) improves hospitalization and health-related quality of life, while reducing long-term mortality [1].

Chronic kidney disease (CKD) is another 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 11% of the total population. CKD patients with HD have a high rate of mortality with cardiovascular diseases, such as chronic heart failure, with a higher mortality risk having been reported for sedentary HD patients [2]. This review focuses on the importance and the efficacy of the rehabilitation of CKD patients as a new target of CR [3].

Correspondence: **Masahiro Kohzuki**, MD, PhD, Professor and Chairman, Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574, Japan, Tel.: +81-22-717-7353, Fax: +81-22-717-7355, E-mail: kohzuki@med.tohoku.ac.jp

The Effect of Regular Exercise in HD 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.

In patients with CKD, exercise endurance is lowered and this phenomenon becomes more distinct as renal dysfunction advances. This is due to the combined effects of uremic acidosis, protein-energy wasting (PEW), and inflammatory cachexia, which lead to and are 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 kidney function decline in CKD [4].

Results from an international study of HD patients indicate that regular exercise is associated with better outcomes in this population and that patients at HD facilities offering exercise programs are more likely to exercise. In a DOPPS study, regular exercisers exhibited higher health-related quality of life, physical functioning and sleep quality scores; reported fewer limitations in physical activities; and were less bothered by bodily pain or a lack of appetite [5]. Regular exercise was also correlated with more positive patient affect and fewer depressive symptoms [5]. In models extensively adjusted for demographics, comorbidities and socio-economic indicators, mortality risk was lower among regular exercisers (hazard ratio=0.73 [0.69–0.78]; P<0.0001) and among more regular exercisers receiving treatment at HD facilities (0.92 [0.89–0.94]; P<0.0001 per 10% more regular exercisers) (Figure 1) [5].

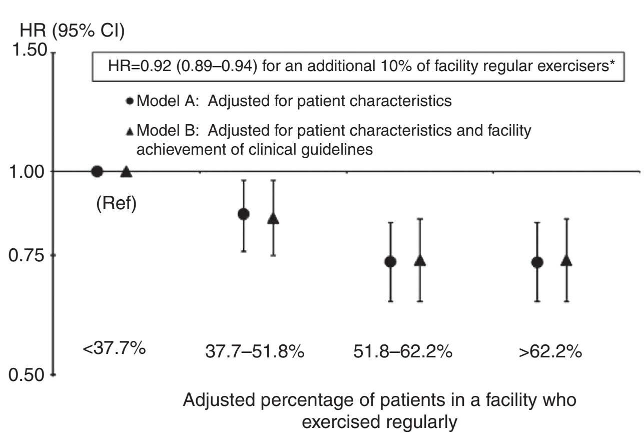

Figure 1 Association between Facility Percentage of Regular Exercisers and Patient Mortality (Ref. [5]).

A meta-analysis of randomized controlled trials reported the effect of regular exercise training for at least 8 weeks in adults with HD [6]. Fifteen studies, comprising 565 patients, were included. At baseline, peak VO_2 values were 70% of age-predicted values. Exercise intervention improved post-training peak VO_2 to 88% of age-predicted values. Exercise training improved peak VO_2 by 25% in eight studies. Significant improvements in lean body mass, quadriceps muscle area, knee extension, hip abduction and flexion strength were also reported [6]. These studies did not find any deaths directly associated with exercise in 28,400 patient-hours and no differences in withdrawal rates between exercise and control participants [6]. Therefore, exercise training is safe and imparts extensive improvements in peak VO_2 in HD patients [6]. Recently, a new systematic review and meta-analysis of randomized controlled trials reported the effects of regular exercise training for at least 8 weeks in adults with CKD stages 2–5, HD patients, or kidney transplant recipients [7]. 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 quality of life were associated with various exercise interventions. Notably, the preponderance of the data collected in these studies was of HD patients and aerobic exercise program participants. Regular exercise training is generally associated with improved health outcomes in individuals with CKD [7]. Moreover, a growing evidence base suggests that exercise training in patients with hemodialysis improves left ventricular function, cardiac sympathetic and parasympathetic disharmony, PEW syndrome, anemia, sleep quality, anxiety, activities of daily living, shunt size, Kt/V and mortality [3, 8].

Barriers to Exercise Participation among HD Patients

The Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines on management of cardiovascular disease state that, "all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" [9].

Delgado et al. [10] administered a 30-item survey regarding exercise counseling to nephrologists attending the American Society of Nephrology (ASN) meeting in 2007. In multivariate analysis, older nephrologists (OR; 95% CI) (3.3; 1.2–9.0) and those more physically active (5.5; 2.0–14) were more likely to ask and counsel patients about physical activity (PA). Opinions associated with less counseling behavior included lack of confidence in ability to discuss PA. Multivariate comparison with previous respondents before the implementation of guidelines indicated that current nephrologists were not asking about PA and did not provide sufficient counseling. Despite guidelines, counseling behavior has not increased. Published guidelines are insufficient to reach younger nephrologists [10]. They also reported that HD patients were interested in physical activity [11]. They reported that most participants strongly agreed that a sedentary lifestyle was a health risk (98%) and that increasing exercise was a benefit (98%). However, 92% of participants reported at least one barrier to physical activity. The most commonly reported barriers were fatigue on HD days and non-HD days and shortness of breath.

In a multivariate analysis, a greater number of reported barriers was associated with lower levels of physical activity. A lack of motivation was associated with less physical activity. Having too many medical problems and not having enough time on HD days were also associated with less activity in an adjusted analysis [11].

Moreover, a larger barrier to the implementation of exercise programs in the HD patients may be the lack of a clearly defined “best” program. The location of exercise training is also an important factor in promoting adherence. In HD patients, intra-dialysis programs have been found to achieve higher adherence rates compared to home exercise programs or supervised programs on non-dialysis days [12].

The Effect of Exercise Training in Animal pre-HD CKD Models

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 glomerular filtration rate. It has also been demonstrated clinically that sudden exercise decreases renal function. There are few reports on the influence of chronic exercise on renal function in animal pre-HD CKD models.

We have published several papers in this field using animal pre-HD CKD models. First, we assessed the renal effects of moderate chronic treadmill exercise in a remnant kidney model of spontaneously hypertensive rats (SHR) with 5/6 nephrectomy and assessed the effects of exercise and antihypertensive therapy on renal function [13]. The rats were divided into four groups: (i) no exercise (No-EX); (ii) moderate exercise with treadmill running (20 m/min, 0 grade incline for 60 min) (EX); (iii) EX with an ACE inhibitor, enalapril (ENA) (2 mg/kg per day, i.p.); and (iv) EX with an angiotensin II receptor antagonist, losartan (LOS) (5 mg/kg per day, i.p.), for 4 weeks. Chronic EX significantly attenuated the increase in proteinuria and significantly protected against increases in the index of glomerular sclerosis (IGS). Both ENA and LOS with EX significantly decreased blood pressure, and further decreased IGS. Exercise, antihypertensive drug, and mean systolic blood pressure remained as significant predictors of mean proteinuria. These results suggest that exercise does not worsen renal function and has renal-protective effects. Moreover, in this model, antihypertensive therapy has additional renal-protective effects [13].

Second, we assessed the renal and peripheral effects of moderate to intense chronic exercise as well as the effects of the combination of chronic exercise and ENA in 5/6-nephrectomized Wistar-Kyoto rats [14]. The rats were divided into six groups according to the following treatment for 12 weeks: (i) no exercise (C); (ii) ENA (2 mg/kg/day, subcutaneously); (iii) moderate exercise with treadmill running (20 m/min for 60 min/day, 5 days/week) (EXm); (iv) intense exercise with treadmill running (28 m/min for 60 min/day, 5 days/week) (EXi); (v) EXm+ENA; and (vi) sham operation (S). Both chronic exercise and ENA blocked the development of hypertension, blunted increases in proteinuria, reduced serum creatinine and blood urea nitrogen, and improved IGS and the relative interstitial volume of the renal cortex (RIV). Moreover, IGS and RIV in the EXm+ENA group were the lowest among all other nephrectomized groups. Furthermore, EXm+ENA enhanced the capillarization and increased the proportion of type-I fibers in the soleus muscle. These results suggest that EX and ENA have renoprotective effects. These findings also suggest that EXm+ENA provided greater renoprotective effects than did ENA alone, and that EXm+ENA exhibited some additional peripheral effects without any complications [14].

Third, we assessed the renal and peripheral effects of chronic exercise in a rat model of diabetic nephropathy (Goto–Kakizaki rats) and the benefits of combined exercise and LOS [15]. The rats were divided into four groups: (i) no exercise (control); (ii) exercise with treadmill running (EX); (iii) LOS; and (iv) EX+LOS, with treatment lasting for 12 weeks. LOS and EX+LOS significantly decreased systolic blood pressure (SBP). EX, EX+LOS, and LOS blunted the increases in proteinuria. IGS and RIV of the renal cortex were significantly improved in the EX, EX+LOS, and LOS groups. The IGS, expressions of ED-1 and a-smooth muscle actin in the glomerulus were the lowest, and the number of Wilms' tumor was the highest in the EX+LOS group. The endurance, the proportion of type I fibers, and capillarization in the extensor digitorum longus muscle were greater in the trained groups. These results suggest that both EX and LOS have renoprotective effects, and that EX+LOS provided greater renoprotective effects than did LOS alone. Further, both EX and LOS may affect macrophage infiltration, mesangial activation, and podocyte loss in this model of diabetic nephropathy. Our results also suggested that exercise has a specific renoprotective effect that is not related to SBP reduction, and can enhance endurance without renal complications [15].

Finally, we evaluated the effects of chronic running exercise on the early stage of diabetic nephropathy by focusing on nitric oxide synthase (NOS), oxidative stress, and glycation in the kidneys of Zucker diabetic fatty (ZDF) rats [16]. 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. 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 ($P<0.01$), while both eNOS and nNOS expression were upregulated by exercise ($P<0.01$). Furthermore, exercise decreased NADPH oxidase activity, p47phox expression ($P<0.01$) and α-oxoaldehyde levels (the precursors for advanced glycation end products) ($P<0.01$) 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 NADPH oxidase and α-oxoaldehyde levels in the kidneys may, at least in part, contribute to renal protective effects of exercise in the early progression of diabetic nephropathy in ZDF rats [16].

In summary, these results suggest that exercise training may have renal protective effects in some animal models of pre-HD CKD.

The Effect of Regular Exercise in pre-HD CKD Patients

There is increasing evidence of the benefit of regular physical exercise in several chronic conditions, including CKD. In patients with cardiovascular disease (CVD) and CKD, it has been reported that exercise therapy for 12 weeks significantly improved the anaerobic metabolic threshold, high-density lipoprotein cholesterol (HDL-C) levels, and estimated glomerular filtration rate (eGFR) [17]. 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, active participation in CR was associated not only with improved peak VO_2, but also with BNP and eGFR in acute myocardial infarction patients with CKD [18].

Moreover, 27 sedentary pre-HD CKD patients (eGFR 27.5±11.6 mL/min) were randomly assigned to a center-based exercise group (n=10), home-based exercise group (n=8) or control group (n=9), with aerobic training being prescribed based upon ventilatory threshold and performed three times per week for 12 weeks [19]. Mean blood pressure decreased in both exercise groups (center-based: 13%, $P<0.01$; home-based: 10%, $P=0.03$) and eGFR increased by 3.6±4.6 mL/min ($P=0.03$) in the center-based group. These parameters remained unchanged in the control group

[19]. Furthermore, Greenwood et al. examined the effect of moderate-intensity exercise training on kidney function and indexes of cardiovascular risk in pre-HD patients with progressive CKD stages 3–4. Single-blind, randomized, controlled, studies showed that 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 [20]. Therefore, exercise therapy could be an effective clinical strategy for improving renal function in pre-HD CKD patients.

Chen et al. reported an association of walking with overall mortality and renal replacement therapy (RRT), such as HD or renal transplant in patients with CKD stages 3–5 [21]. 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 (SHR) 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 [21].

What is Renal Rehabilitation?

Urgent efforts should be made to increase the implementation rate of RR. We have established the Japanese Association of Renal Rehabilitation in 2011 to evaluate and promote RR. We published the first book titled, "Renal Rehabilitation," in the world [8]. We define RR 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. RR includes five major components: exercise training, diet, and fluid management, medication and medical surveillance, education, psychological and vocational counseling" [3, 8]. Exercise therapy can be an effective clinical strategy for improving renal function and lower RRT risk in pre-HD CKD patients. Recently, the Ministry of Health, Labor and Welfare of Japan became the first country in the world to extend RR partial coverage to patients with stage 4 pre-HD CKD patients.

Adding Life to Years and Years to Life

In the context of our aging population, the number of people with multiple morbidities and disabilities (MMD) as well as their needs for rehabilitation have increased rapidly beyond what was expected [22]. Medical science has sought to "add years to life" by increasing life expectancy. Rehabilitation generally seeks to "add life to years" by helping patients with impairment achieve and use their full physical, mental and social potential. However, recent growing evidence suggests that rehabilitation for patients with visceral impairment, such as cardiac, renal and pulmonary impairment, can not only improve exercise performance and quality of life, but also increase their chances of survival (Figure 2) [23]. Therefore, modern comprehensive rehabilitation for patients with visceral impairment does not simply "add life to years," but indeed "add

Medicine and Rehabilitation
- Medicine ➔ Adding Years to Life
- Rehabilitation ➔ Adding Life to Years

Renal Rehabilitation (⊂ Visceral Rehabilitation)
➔ Adding Life to Years and Years to Life

Figure 2 Renal Rehabilitation is a New Target of Cardiac Rehabilitation (Ref. [23]).

life to years and years to life," which is a new concept in rehabilitation [23].

Conclusion and Take-Home Message

This review focuses on the importance and efficacy of rehabilitation for CKD patients as a new target of CR. We should improve not only the quality of life, but also the biological lifespan of patients with CKD. RR is a feasible, effective, and safe secondary prevention strategy following CKD, and offers a promising model for the new field of rehabilitation. Future RCTs 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.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This work was supported by JSPS KAKENHI Grant Number 26282153, 16K12925.

REFERENCES

1. Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal HM, Lough F, et al. Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. Open Heart 2015;2(1):e000163.
2. O'Hare AM, Tawney K, Bacchetti P, Johansen KL. Decreased survival among sedentary patients undergoing dialysis: results from the dialysis morbidity and mortality study wave 2. Am J Kidney Dis 2003;41:447–54.
3. Kohzuki M. Renal rehabilitation: present and future perspectives. In: Suzuki H, editor. Hemodialysis. Rijeka, Croatia: Intech; 2013. pp. 743–51.
4. Johansen KL. Exercise in the end-stage renal disease population. J Am Soc Nephrol 2007;18:1845–54.
5. Tentori F, Slder SJ, Thumma J. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. Nephrol Dial Transplant 2010;25:3050–62.
6. Smart N, Steele M. Exercise training in haemodialysis patients: a systematic review and meta-analysis. Nephrology 2011;16:626–32.
7. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. Am J Kidney Dis 2014;64(3):383–93.
8. Kohzuki M. Renal rehabilitation: difinition and evidence. In: Kohzuki M, editor. Renal rehabilitation. Tokyo: Ishiyaku Publishers, Inc.; 2012. pp. 10–7.
9. K/DOQI Workshop. K/DOQI clinical practice guidelines dor cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45 (Suppl 3):S1–153.
10. Delgado C, Johansen KL. Deficient counseling on physical activity among nephrologists. Nephron Clin Pract 2010;116:cc336, 330.
11. Delgado C, Johansen KL. Barriers to exercise participation among dialysis patients. Nephrol Dial Transplant 2012;27:1152–7.
12. Konstantinidou E, Koukouvou G, Kouidi E, Deligiannis A, Tourkantonis A. Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. J Rehabil Med 2002;34:40–5.
13. Kohzuki M, Kamimoto M, Wu XM, Xu HL, Kawamura T, Mori N, et al. Renal protective effects of chronic exercise and antihypertensive therapy in hypertensive rats with chronic renal failure. J Hypertens 2001;19:1877–82.
14. Kanazawa M, Kawamura T, Li L, Sasaki Y, Matsumoto K, Kataoka H, et al. Combination of exercise and enalapril enhances renoprotective and peripheral effects in rats with renal ablation. Am J Hypertens 2006;19:80–6.
15. Tufescu A, Kanazawa M, Ishida A, Lu H, Sasaki Y, Ootaka T, et al. Combination of exercise and losartan enhances renoprotective and peripheral effects in spontaneously type 2 diabetes mellitus rats with nephropathy. J Hypertens 2008;26:312–21.
16. Ito D, Cao P, Kakihana T, Sato E, Suda C, Muroya Y, et al. Chronic running exercise alleviates early progression of nephropathy with upregulation of nitric oxide synthases and suppression of glycation in zucker diabetic rats. PLoS One 2016;10(9):e0138037.
17. Toyama K, Sugiyama S, Oka H, Sumida H, Ogawa H. Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. J Cardiol 2010;56:142–6.
18. Takaya Y, Kumasaka R, Arakawa T, Ohara T, Nakanishi M, Noguchi T, et al. Impact of cardiac rehabilitation on renal function in patients with and without chronic kidney disease after acute myocardial infarction. Circ J 2014;78:377–84.

19. Baria F, Kamimura MA, Aoike DT, Ammirati A, Rocha ML, de Mello MT, et al. Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients. Nephrol Dial Transplant 2014;29:857–64.
20. Greenwood SA, Koufaki P, Mercer TH, MacLaughlin HL, Rush R, Lindup H, et al. Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: a pilot randomized controlled trial. Am J Kidney Dis 2015;65:425–34.
21. Chen IR, Wang SM, Liang CC, Kuo HL, Chang CT, Liu JH, et al. Association of walking with survival and RRT among patients with CKD stages 3–5. Clin J Am Soc Nephrol 2014;9:1183–9.
22. Kohzuki M. Paradigm shift in rehabilitation medicine in the era of multimorbidity and multiple disabilities (MMD). Phys Med Rehabil Int 2014;1(2):id1006.
23. Kohzuki M, Sakata Y, Kaweamura T. A paradigm shift in rehabilitation medicine: from “Adding Life to Years” to “Adding Life to Years and Years to Life”. Asian J Human Services 2012;2:1–8.