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Renal Rehabilitation: Present and Future Perspectives

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<http://dx.doi.org/10.5772/52909>

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. In patients with CKD, exercise endurance, measured as maximal oxygen uptake (VO_2 max), etc. is lowered and this phenomenon becomes more distinct as the renal dysfunction advances. Poor physical condition and skeletal muscle wasting are associated with CKD. This is due to the combined effects of uremic acidosis, protein-energy malnutrition and inflammatory cachexia, which lead to and are further aggravated by a sedentary lifestyle. Together, these factors result in a progressive downward spiral of deconditioning.

Renal rehabilitation (RR) is 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: such as exercise training, diet & fluid management, medication & medical surveillance, education, psychological & vocational counseling. Present and future perspectives of RR is addressed in this chapter.

2. Physical inactivity in CKD patients

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

Patients with end-stage renal disease (ESRD) on maintenance haemodialysis have very high mortality, and yet higher mortality risk has been reported for sedentary hemodialysis patients [1]. As well as being a strong cardiovascular risk factor, physical inactivity is associated with increased risk of rapid kidney function decline in CKD [2].

Unfortunately the role of physical activity in renal disease has been largely overlooked and provision of exercise advice and rehabilitation programs for kidney patients lags well behind that of cardiology and pulmonary services. Levels of physical exercise among CKD patients with hemodialysis are low. Regular exercise frequency varied widely across countries and across dialysis facilities within a country.

3. The effect of regular exercise in dialysis CKD patients

The positive effects of physical exercise reported in the general population may be highly relevant for ESRD patients. Increased physical activity has been associated with improved ability and capacity to perform activities in everyday life, occupational tasks, health-related quality of life and survival. Therefore regular exercise is recommended to this population.

Results from an international study of haemodialysis patients indicate that regular exercise is associated with better outcomes in this population and that patients at facilities offering exercise programs have higher odds of exercising. In DOPPS study, overall, 47.4% of participants were categorized as regular exercisers. The odds of regular exercise was 38% higher for patients from facilities offering exercise programs ($P = 0.03$) [3].

In DOPPS study, regular exercisers had 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 lack of appetite. Regular exercise was also correlated with more positive patient affect and fewer depressive symptoms. 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 at facilities with more regular exercisers (0.92 [0.89–0.94]; $P < 0.0001$ per 10% more regular exercisers) [3].

A systematic literature search was completed in August 2010 to identify randomized, controlled trials of exercise training studies in hemodialysis patients. A subsequent meta-analysis was conducted and the search repeated in December 2010 [4]. Fifteen studies, yielding 565 patients were included. Baseline, peak VO_2 values were 70% of age-predicted values, exercise intervention patients improved post-training peak VO_2 to 88% predicted. Exercise training produced 26% improvements in eight studies that reported peak VO_2 . Equivocal results for change in short-form 36 health questionnaire scores were reported post-training. Significant improvements in lean body mass, quadriceps muscle area, knee extension, hip abduction and flexion strength were also reported [4]. They 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. Exercise training for 6 months or more conveyed larger improvements in peak VO_2 than shorter programs. Therefore, Exercise training is safe and imparts large improvements in peak VO_2 , and heart rate variability in hemodialysis patients [4].

Moreover, a growing evidence base suggests that exercise training in patients with hemodialysis improves in $\text{VO}_{2\text{max}}$, left ventricular function, cardiac sympathetic and parasympa-

thetic disharmony, malnutrition-inflammation-atherosclerosis syndrome, anemia, sleep quality, anxiety, health-related quality of life, activities of daily living, shunt size, Kt/V and mortality [5]. In contrast, a recent randomized clinical trial failed to show further benefits of additional resistance exercise on long-term somatic protein accretion above and beyond nutritional supplementation alone [6]. Further research is necessary to both understand the observed lack of obvious benefits and strategies to improve the exercise regimens in patients with hemodialysis.

4. Low implementation rate of exercise therapy or rehabilitation for patients with visceral impairment

Therefore regular exercise is recommended to haemodialysis patients.

The problem of exercise therapy or rehabilitation for patients with visceral impairment such as renal or cardiac impairment is a low implementation. Because the beneficial effects of rehabilitation on exercise capacity, quality of life, and prognosis (mortality) in patients with visceral impairment have been established, the low implementation rate of rehabilitation implies that patients are kept away from the established benefits of rehabilitation by reasons unrelated to the patient conditions. Thus, efforts should be made urgently to increase the implementation rate of rehabilitation.

Why, then, have exercise and rehabilitation not been broadly applied? For example, the cardiac rehabilitation (CR) program usually consists of three stages: the acute stage (phase I), subacute stage (stage II) and maintenance stage (phase III). Phase III CR is recognized as a community or home-based program committed to encourage exercise and a healthful lifestyle with the goal of minimizing the risk of recurring cardiac problems (secondary prevention). A recent study [7] demonstrated that the participation rate of phase II CR to be 12% in the Japanese Circulation Society (JCS)-authorized cardiology-training hospitals (TH) and 5% in all the hospitals in Japan. Major reasons for not implementing CR were lack of staff, equipment and space, and the absence of the approval for the CR facility standards [7]. However, THs are usually large-sized, general hospitals which would be expected to have sufficient staff, equipment, and space. In addition, 73% of THs that had been approved for specific intensive care did not have an approval for CR despite their ability to fulfill the CR facility standards indicates that there should be reasons other than the CR facility standards for the non-implementation of CR in these hospitals [7].

Ades et al [8] reported that by multivariate analysis, the strength of the physician's recommendation for participation was the most powerful predictor of cardiac rehabilitation entry in patients after acute myocardial infarction (AMI) or coronary bypass surgery. Thus, physicians' reluctance or lack of proper understanding to use CR after AMI might be the reason for the low implementation rate of CR in Japan. Since the CR facility standards in Japan has been loosened in 2004, 2006, and 2010, the motivation of physicians and hospitals would be a critically important factor for the implementation of CR [9].

5. Barriers to exercise participation among dialysis patients

The recently published 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” [10].

Delgado et al. [11] 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 to previous respondents before the guidelines showed current nephrologists were not asking and counseling more. Despite the guidelines, counseling behavior has not increased. Published guidelines are insufficient to reach younger nephrologists [11]. They also reported that dialysis patients were interested in physical activity [12]. They reported that the majority of 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 dialysis days and non-dialysis days and shortness of breath. In multivariate analysis, a greater number of reported barriers was associated with lower levels of physical activity. Lack of motivation was associated with less physical activity. Endorsement of too many medical problems and not having enough time on dialysis days were also associated with less activity in adjusted analysis [12].

Perhaps a larger barrier to implementation of exercise programs in the dialysis population is the lack of a clearly defined “best” program. The location of the exercise training is also an important factor influencing adherence. In HD patients, intradialytic programs have been found to achieve higher adherence rates compared to home exercise programs or supervised programs on nondialysis days [13]. Dialysis facility efforts to increase patient physical activity may be beneficial. Studies of the barriers to patient participation in exercise and to provider assessment and recommendations are needed so that more widely generalisable interventions can be developed.

6. The effect of exercise training in predialysis CKD patients

There is increasing evidence of the benefit of regular physical exercise in a number of long-term conditions including chronic kidney disease (CKD). However, this evidence has mostly come from studies in end stage patients receiving regular dialysis. It should be noted that the majority of published studies were small and enrolled patients were undergoing hemodialysis. Relatively few studies have included patients with stage 1 to 4 CKD, which limits the generalization of findings to predialysis CKD patients.

It is also necessary to consider the influence of exercise on renal functions because acute exercise causes proteinuria and subsequent reductions in both the 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 and there is little information about the effect of exercise on predialysis CKD patients. The optimal intensity and duration of exercise for patients with chronic renal failure has not yet been formulated.

Recently, it is reported that exercise therapy for 12 weeks significantly improved the anaerobic metabolic threshold and high-density lipoprotein cholesterol (HDL-C) levels, and estimated glomerular filtration rate (eGFR) in patients with cardiovascular disease (CVD) and CKD [14]. Change in eGFR correlated significantly and positively with change in anaerobic metabolic threshold and HDL-C. Exercise therapy correlates with improving renal function in CVD patients with CKD through modifying lipid metabolism. Therefore, exercise therapy could be an effective clinical strategy to improve renal function.

7. The effect of exercise training in animal predialysis CKD models

Also, there are few reports about the effect of exercise on renal function in animal models of chronic renal failure. We have been published several papers in this field recently.

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 also assessed the effects of exercise and antihypertensive therapy on renal function [15]. The rats were divided into four groups: (i) no exercise (Non-EX); (ii) moderate exercise with treadmill running (20 m/min, 0 grade incline for 60 min) (EX); (iii) EX with an angiotensin converting enzyme (ACE) inhibitor, enalapril (2 mg/kg per day, i.p.); and (iv) EX with an angiotensin receptor antagonist, losartan (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 enalapril and losartan with EX significantly decreased blood pressure, and further decreased the IGS. In the stepwise multiple regression analysis, only antihypertensive drug remained in the model as a significant predictor of IGS. In contrast, exercise, antihypertensive drug and mean systolic blood pressure remained in the model as a significant predictors of mean proteinuria. These results suggest that exercise does not worsen renal function and has renal-protective effects in this model of rats. Moreover, the antihypertensive therapy has additional renal-protective effects in this model of rats.

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 enalapril (ENA) in 5/6-nephrectomized Wistar-Kyoto rats [16]. The rats were divided into six groups according to the following treatment: 1) no exercise (C); 2) ENA (2 mg/kg/day, subcutaneously); 3) moderate exercise with treadmill running (20 m/min for 60 min/day, 5 days/week) (EXm); 4) intense exercise with treadmill running (28 m/min for 60 min/day, 5 days/week) (EXi); 5) EXm

+ENA; and 6) sham operation (S). The rats were then treated for 12 weeks. 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 capillarization as well as the proportion of type-I fiber in the soleus muscle. These results suggest that EX and ENA have renoprotective effects. The findings also suggest that EXm+ENA provided greater renoprotective effects than those of ENA alone, and that EXm+ENA had some additional peripheral effects without any complications in this rat model.

We also assessed the renal protective effects of treatment with moderate exercise (EX; 20 m/min for 60 min/day, 5 days/week), with EX plus angiotensin II receptor antagonist olmesartan (OLS), with EX plus calcium channel blocker amlodipine (AMN), and with the three together in 5/6-nephrectomized Wistar Kyoto rats for 12 weeks [17]. EX, EX+OLS, EX+AMN, and EX+OLS+AMN showed decreases in the serum creatinine (Scr), an index of glomerular sclerosis (IGS), the relative interstitial volume of the renal cortex (RIV), the number of ED-1 (monoclonal antibody) positive cells (ED1(+)) and the glomerular expression score of α -smooth muscle actin (α -SMA(+)). EX+OLS, EX+AMN, and EX+OLS+AMN blocked the development of hypertension, increased the number of Wilms' tumor-1 (WT-1) positive cells (WT1(+)); EX+OLS and EX+OLS+AMN blunted the increases in proteinuria. In particular, blood urea nitrogen (BUN), ED1(+), α -SMA(+), WT1(+), IGS, and RIV in the EX+OLS+AMN were the lowest among all the nephrectomized groups. In the results, simultaneous treatment of EX, OLS, and AMN showed renal protective effects in this rat model suggesting that the treatment may affect the macrophage infiltration to the glomerulus, the fibroblast accumulation in the glomerulus, the mesangial activation, and the podocyte differentiation.

Finally, 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 losartan [18]. The rats were divided into four groups: (i) no exercise (control); (ii) exercise with treadmill running; (iii) losartan; (iv) exercise plus losartan, and the rats were treated for 12 weeks. Losartan and exercise plus losartan significantly decreased systolic blood pressure (SBP). Exercise, exercise and losartan, and losartan blunted the increases in proteinuria. IGS and RIV of the renal cortex were significantly improved in the exercise, exercise and losartan, and losartan groups. The IGS, expressions of ED-1 and α -smooth muscle actin in the glomerulus were the lowest, and the number of Wilms' tumor was the highest in the exercise plus losartan group. The endurance, the proportion of type I fibre and capillarization in the extensor digitorum longus muscle were greater in the trained groups. These results suggest that both exercise and losartan have renoprotective effects, and the combination of exercise and losartan provided greater renoprotective effects than losartan alone, and may affect macrophage infiltration, mesangial activation, and podocyte loss in this model of diabetic nephropathy. It is also suggested that exercise has a specific renoprotective effect that is not related to SBP reduction, and can enhance endurance without renal complications.

Exercise training does not always show renoprotective effect in any animal models of predialysis CKD. For example, we reported that exercise training did not show renoprotective effect in Thy-1 nephritis model and adriamycin-induced nephritic syndrome model [19,20].

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

8. What is renal rehabilitation?

Moreover, we have established the Japanese Association of Renal Rehabilitation in 2011 to evaluate and promote renal rehabilitation (RR). We define RR as, "RR is coordinated, multi-faceted 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: such as exercise training, diet & fluid management, medication & medical surveillance, education, psychological & vocational counseling." [21]. The first step to successful RR is ensuring that the clinical prerequisites of anemia control, adequate dialysis, exercise, a well-functioning vascular access, and proper nutrition are in place. The Life Options Rehabilitation Advisory Council (LORAC) developed a comprehensive approach to RR, based on the "5E's:" Encouragement, Education, Exercise, Employment, and Evaluation [22].

9. Adding life to years and years to life

Medical science basically aims to "Adding Years to Life" by increasing life expectancy. Rehabilitation generally aims to "Adding 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 increases survival [23]. Therefore, modern comprehensive rehabilitation for patients with visceral impairment does not simply aim to "Adding Life to Years" but "Adding Life to Years and Years to Life" which is a new rehabilitation concept [23].

10. Conclusion

In RR, we should improve not only quality of life but also biological lifespan in patients with CKD. RR is a feasible, effective and safe secondary prevention strategy following CKD, and offers a promising model for 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. Moreover, efforts should be made urgently to increase the implementation rate of the RR.

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