Exercise Therapy Correlates with Improving Renal Function through Modifying Lipid Metabolism in Patients with Cardiovascular Disease and Chronic Kidney Disease

– A pilot study of exercise training and renal dysfunction -

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Abstract

Background: Patients with cardiovascular disease (CVD) and chronic kidney disease (CKD) are at high risk of cardiovascular mortality, thus therapies to improve renal function should be clinically investigated.

Methods and Results: We divided consecutive patients with CVD and CKD (n=19) into exercise (n=10) and non-exercise (n=9) therapy groups. Exercise therapy for 12 weeks significantly improved the anaerobic metabolic threshold (AT-$\dot{V}$O2) and high-density lipoprotein cholesterol (HDL-C) levels, and reduced triglyceride levels. Exercise therapy also improved estimated glomerular filtration rate (eGFR). Change in eGFR correlated significantly and positively with change in AT-$\dot{V}O_2$ and HDL-C, and negatively with change in triglyceride levels.

Conclusions: Exercise therapy correlates with improving renal function in CVD patients with CKD through modifying lipid metabolism. Exercise therapy could be an effective clinical strategy to improve renal function.

Key words: Kidney, Cardiovascular Disease, Rehabilitation, Lipids

Introduction

Patients with cardiovascular disease (CVD) and chronic kidney disease (CKD) are at high risk of cardiovascular mortality[1], thus therapies designed to prevent or improve renal function are clinically important. While the importance of cardiac rehabilitation is recognized in recent clinical cardiovascular therapies, we have experienced several CVD patients with CKD who later showed improvement of renal function in the real clinical practices. Several animal studies have demonstrated the beneficial effects of exercise training on renal function[2, 3], and Moinuddin I et al. recently showed that aerobic exercise increase eGFR in CKD patients[4].

Dyslipidemia is an independent risk factor for both CVD and CKD. Recent study reported dyslipidemia accelerates the risk for CKD[5], thus we especially focus on the relationship between serum levels of lipid parameters and renal function. The beneficial effects of exercise therapy on lipid metabolism in patients with CVD were also reported recently[6]. The hypothesis tested in this study was that scheduled exercise training improves renal function associated with changes in serum lipids in CVD patients with CKD.

Methods

The study protocol was approved by the Institutional Review Board and written informed consent was obtained from each patient. This prospective open-labeled clinical trial included consecutive 19 CVD patients with CKD (age=71.7±11.0, mean±SD, 89% male, 89.5% ischemic heart disease, ejection fraction 59.0±10.8%) divided into the exercise training (ET) group (n=10, estimated glomerular filtration rate [eGFR]; 47.0±13.7 ml/min/1.73 m^2) and non-exercise training (non-ET) group (n=9, eGFR; 47.9±9.6 ml/min/1.73 m^2). Consecutive patients with CVD and CKD (eGFR $\leq$ 60 ml/min/1.73m^2) who agree to join cardiac rehabilitation therapy were allocated to ET group, and consecutive outpatients with CVD and CKD without daily habits of exercise were allocated to non-ET group. Exclusion criteria were: impossible to exercise; proteinuria $\geq$ 1g/day; rapidly progressive glomerulonephritis; nephrotic syndrome; HbA1c $\geq$ 8.0%; left ventricular ejection fraction < 30%; history of low pulmonary function and lung disease; history of hepatic and renal disturbance.

Patients of the ET group performed once-a-week in-hospital aerobic exercise (half-hour bicycle ergometer) and home exercise (half-hour daily walking referring to Borg index at 12-13) for 12 weeks. Also both groups equally performed comprehensive intervention including diet therapy, mental support, counseling for medication, educations for cardiovascular disease except for exercise intervention. In addition, at study entry and 12 weeks later, all patients underwent blood sampling and cardiopulmonary exercise tests to determine the anaerobic metabolic threshold (AT-$\dot{V}O_2$), one of the criteria of cardiopulmonary function. The eGFR was calculated using an equation from the Modification Diet in Renal Disease Study for the Japanese population.

Cardiopulmonary Exercise Test

Individually-optimized 5, 10, 15, 20watt-up ramp protocol exercise on an electromagnetically braked cycle ergometer (Well Bike BE-250, CATEYE CO. , LTD.) with blood pressure and heart rate monitoring was performed. Respiratory gas was sampled from a mouthpiece, and minute ventilation, carbon dioxide output, oxygen uptake, ventilatory equivalent for carbon dioxide, ventilatory equivalent for oxygen were obtained breath by breath (METAMAX3B, KYOKKOUBUSSAN CO., LTD.). Using above parameters, the single operator of medical technologist who was blinded to each treatment group calculated anaerobic metabolic threshold (AT- $\dot{V}O_2$), criteria of exercise tolerance, and cardiopulmonary function.

Statistical analysis

All statistical analyses were carried out using SPSS statistical software, version 11.0J (SPSS Inc., 233 South Wacker Drive, 11th floor, Chicago, IL 60606-6412). To compare the baseline characteristics of the two groups, data were analyzed by Student’s t-test for unpaired data and Fisher’s exact test for categorical data. To analyze treatment effect over 12weeks, a paired Student’s t-test was performed. Association between eGFR and each AT- $\dot{V}O_2$, triglyceride and high-density lipoprotein cholesterol (HDL-C) was assessed using Person’s correlation coefficient. Hazard ratios, 95% confidence intervals, and levels of statistical significance (P value) were calculated. To determine the association between improvement in eGFR, and each the change in HDL-C levels and exercise therapy, we adjusted for age and the change in triglyceride levels in the following multivariable liner regression analysis by the forced inclusion models; Model 1 included age, the change in triglyceride and HDL-C levels; Model 2 included age, the change in triglyceride, and exercise therapy. Data were expressed as mean $\pm$ standard deviation and $p<0.05$ was considered statistically significant.

Results

There were no significant differences in sex, age, medications, coronary risk factors, cardiac ultrasound parameters and AT-$\dot{V}O_2$ between the two groups at study entry (Table 1). Also baseline of renal function and lipid parameters are not significantly different. Regular exercise for 12 weeks significantly improved AT-$\dot{V}O_2$ (Figure 1a), and significantly changed all lipid parameters, increase in HDL-C and decrease in triglyceride and LDL-C within normal limits (Figure 1b-d). On the other hand, exercise had no significant effect on arterial blood pressure and hematocrit levels in both groups. Exercise significantly improved eGFR in the ET group (47.0±13.7 to 55.2±16.9 ml/min/1.73 m^2, p=0.021) but we could not find any change in eGFR in the non-ET group (47.9±9.5 to 44.6±8.2 ml/min/1.73 m^2, p=0.082). There was a significant difference in the change of eGFR between the two groups (Figure 2a). The change in eGFR correlated significantly and positively with the change in AT-$\dot{V}O_2$ (r=0.785, p<0.001, Figure 2b).

Renal Function and Lipid Parameters

The change in eGFR correlated significantly and positively with the change in HDL-C (r=0.535, p=0.018, Figure 2d), and negatively with the change in triglyceride (r= -0.513, p=0.025, Figure 2c). Two patients in ET group showed remarkable increase in HDL-C levels, one patient demonstrated HDL-C increased from 46mg/dl to 95mg/dl and another patient demonstrated from 44mg/dl to 78mg/dl without reduction in body weight, change in dietary habit and life style except for the exercise intervention. Each change in HDL-C (β=0.482, $p=0.045$) and exercise intervention (β=0.676, $p=0.006$) significantly associated with an increase in eGFR levels in adjusted multiple regression analysis for age and change in triglyceride.

Discussion

Most patients with CKD and CVD tend to be forced to live in limited activity. Although exercise is not strongly recommended clinically for CKD patients, our study demonstrated the beneficial effects of exercise training, especially on renal function, in patients with CVD and CKD.

It is reported that CKD patients typically show high triglyceride and low HDL-C levels and this accelerates the progression of CKD[7, 8]. Several experimental studies in hyper-lipid CKD mice[9, 10] reported that dyslipidemia contributes to renal tissue injury such as glomerulosclerosis, by increasing reactive oxygen species-induced activation of nuclear factor kappa B and subsequent elevation of interleukin-6. In general, exercise increases HDL-C and decreases triglyceride levels[11], and our present study demonstrated similar results. Serum HDL-C increase has been shown to contribute to renal function improvement[12], and thus elevating HDL-C levels by exercise therapy could improve renal function in CKD patients. It is also reported that exercise can prevent progressive renal dysfunction through improvement of hyperlipidemia in nephritic rat model[3]. Multivariate regression analysis demonstrated the independent association between the increase in HDL and improvement of eGFR in the present study, indicating the importance of elevating HDL by exercise therapy. Our data suggest the potential clinical benefits that regular exercise with increased cardiopulmonary function can correlate with improving renal function through modifying lipids metabolism, particularly HDL elevation.

The contribution of the change in blood pressure for the improvement of eGFR is not denied, however our results showed no significant change in blood pressure in the ET and non-ET groups. Unfortunately, albuminuria, an independent risk factor of CVD, and other metabolic parameters were not analyzed properly in the present pilot study, and thus effects of exercise therapy on these parameters and renal functions need to be determined in the future studies.

Limitations

There are several limitations to the present study. First, this study had a small sample. Second, the baseline levels of HDL-C in ET group were apparently lower than non-ET group. However, the change in levels of HDL-C significantly associated with the change in eGFR in adjusted multiple regression models forced including the baseline levels of HDL-C (β=0.589, p=0.017). Therefore, there are no significant association with the difference in baseline levels of HDL-C and the present primary results.

To conclude more sufficient importance associated with exercise and renal function, further large trials are required. However, the aim of this pilot study was to determine the beneficial effects between exercise and renal dysfunction, and we believe the present study is a valuable report promoting further investigation.

Conclusion

Our 12-week exercise intervention resulted in significant improvement in renal function in CVD patients with CKD. This improvement was partially correlated with modifying lipid metabolism and cardiopulmonary function. Exercise therapy could be an effective clinical strategy to prevent cardiovascular complications through the additional benefits on renal function.

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Figure legends

Table 1: Baseline Characteristics. There is not significant difference in baseline characteristics between two groups at study entry in all parameters.

Figure 1: Changes in AT-VO2 and lipid parameters. Regular exercise significantly improved AT-$\dot{V}$O2 (a) and modified lipid parameters (b-d). Data are mean±SD.

Figure 2: Changes in eGFR and each parameters showing significant correlation with eGFR; (a) Regular exercise significantly improved eGFR compared to non-ET group. (b) Correlation between the change in AT-$\dot{V}O_2$ and eGFR, (c) in triglyceride and eGFR and (d) in HDL-C and eGFR. The curved lines in b-d represent ±2SD values of the regression line. Closed circle shows ET group, and open circle shows non-ET group.