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Editorial

Acute intradialytic exercise and oxidative stress in hemodialysis patients

Patients with chronic kidney disease (CKD) receiving maintenance hemodialysis (HD) have diminished muscle mass, altered muscle quality, and severely impaired capacity for physical work and exercise tolerance, which has been reported to be as low as 50% of that measured in age-matched healthy individuals [1]. Uremic toxins, anemia, metabolic acidosis, vitamin D deficiency, hyperparathyroidism, and inflammation are among the possibilities; any or all of these could act to cause muscle wasting and/or altered neuromuscular function in dialysis patients [2]. Physical inactivity exacerbates these functional declines and also promotes cardiovascular disease (CVD). This cycle of disease and disability greatly reduces the quality of life (QOL) and increases mortality rates in these patients [3].

There are abundant studies demonstrating the benefits from physical exercise training in CKD patients. Regular exercise leads to increased exercise capacity, improved health-related QOL, and decreased morbidity. Exercise may reduce cardiovascular risk through its beneficial effects on blood pressure, lipid profile, insulin resistance, and glycemic control. In end stage renal disease (ESRD) patients, exercise has also been shown to improve arterial stiffness, blood pressure, cardiorespiratory function, and QOL. A recently published systematic review and meta-analysis of controlled trials investigating the efficacy of exercise showed that exercise improves aerobic capacity, muscle strength, cardiovascular function, and health-related QOL in patients with CKD [4].

Recognizing this, the recent Kidney Disease: Improving Global Outcomes (KDIGO) CKD clinical practice guideline recommends that patients with CKD undertake regular physical activity, compatible with cardiovascular health and tolerance, aiming for at least 30 minutes five times per week [5]. However, physical exercise appears to be poorly prescribed in nephrology practice. Many reasons may exist for this oversight, including lack of time for exercise counseling, insufficient knowledge among nephrology staff about optimal exercise to prescribe to patients, or uncertainty about how to prescribe and adapt exercise interventions. In addition, many of dialysis patients have decades of sedentary behavior and comorbid conditions that make a generic approach to exercise prescription likely to fail [6].

In an attempt to promote exercise adoption, several investigators have prescribed exercise training during routine HD treatment (the intradialytic exercise). Maintenance HD is a time-consuming and regular treatment that is routinely performed at least 3–5 h/d, two or three times a week under care of medical staff. Even though there are many debates about the beneficial effects of the intradialytic exercise, it improves exercise adoption and adherence in these patients. Therefore, various exercise programs, such as aerobic exercise, resistance exercise, combined aerobic and resistance exercise, and passive exercise including electrical stimulation have been developed for HD patients [7].

The intradialytic exercise programs are mostly composed of aerobic exercises such as cycle ergometer or bicycle training. The exercise programs are variable, using different exercise frequencies, intensities, and duration, but mostly consists of two or three times a week (during HD), with moderate or vigorous intensity for 30 minutes or more. The resistance exercise programs are available for dialysis patients: progressive resistance training of upper extremity strengthening with free-weight dumbbells, lower extremity strengthening with weighted ankle cuffs, or use of the Thera-band stretch strap and other specific progressive resistance training for shoulder, hip, and abdominal musculature [8].

The most common risk of exercise participation is musculoskeletal injury that may be increased in dialysis patients as a result of hyperparathyroidism and bone disease. Furthermore, the most serious risks are those of cardiac origin, ranging from dysrhythmia to ischemia to sudden death, and all patients with ESRD or advanced CKD. Although no serious exercise-induced adverse events have been reported in most of the published trials of the intradialytic exercise training conducted with HD patients, these studies were undertaken in relatively healthy dialysis patients, therefore, these beneficial effects of intradialytic exercise could not be extrapolated to all dialysis patients.

CVD is not only the most common cause of mortality among patients receiving dialysis but is also a major source of morbidity and mortality among patients with CKD. Many potential mediators of this increased risk have been proposed, including an increased prevalence of traditional risk factors, such as hypertension, diabetes, and dyslipidemia, as well as other factors that may relate more directly to reduced kidney function, such as endothelial dysfunction, increased sympathetic

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activity, oxidative stress, and inflammation. Several of these candidate mediators are potentially ameliorated by exercise interventions. No studies in CKD patients have been carried out to establish the impact of exercise on cardiovascular outcomes, however, a few studies have examined the effects of exercise on potential mediators of cardiovascular risk. Oxidative stress may be defined as a disturbance in regular cellular and molecular function caused by an imbalance between production of reactive species and the natural antioxidant ability. Excessive oxidative stress associated with uremia is believed to play a critical role in the development of chronic inflammation in CKD patients; oxidative stress and inflammation both play a significant role in CVD development in CKD patients.

The long-term exercise training improved arterial stiffness [9] and exerted anti-inflammatory effects (reduction in the ratio of plasma interleukin-6 to interleukin-10 levels) and a downregulation of T-lymphocyte and monocyte activation in CKD patients [10]. Water-based exercise intervention may reduce blood pressure and oxidative stress, indicated by a decrease in products of lipid peroxidation and an increase in reduced glutathione [11]. In ESRD patients, chronic intradialytic exercise training may improve CVD risk by decreasing novel risk factors including serum oxidative stress, alkaline phosphatase, and epicardial fat [3]. However, there is limited information regarding the effects of acute intradialytic exercise on oxidative stress responses in HD patients.

In the current issue of *Kidney Research and Clinical Practice*, Esgalhado et al [12] assess the effect of single session of intradialytic strength physical exercise on oxidative stress and inflammatory responses in HD patients. They compared the level of plasma antioxidant enzymes [superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)], malondialdehyde, and high-sensitivity C-reactive protein levels on two different days with exercise and without exercise at 30 minutes and 60 minutes after starting the HD in the same patients. The present study did not show significant differences in plasma catalase, GPx, malondialdehyde, and high-sensitivity C-reactive protein, but the plasma SOD level was increased on nonexercise days, although it was decreased after acute strength physical exercise. They explained these results by suggesting that suboptimal increased production of SOD failed to compensate excessive production of free radicals formed from the intradialytic exercise: it may lead to a reduction in plasma SOD levels. The main finding of the present study is that acute intradialytic exercise was unable to reduce oxidative stress and inflammation, and in addition, it seems that reduced plasma SOD levels may exacerbate oxidative stress in these patients.

Data regarding oxidative stress levels after acute physical exercise in dialysis patients are very limited. A previous study examined the effects of acute cardiovascular exercise on oxidative stress in HD patients, HD exhibited higher oxidative markers (thiobarbituric acid-reactive substances and protein carbonyls) at rest, and exercise elicited a marked increase of oxidative stress markers, these changes were more pronounced in HD patients than in the healthy control group [13]. This exacerbation of oxidative stress in HD patients with exercise may be attributed to their reduced antioxidant capacity both at rest and during exercise. The differences between the two studies may lead to conflicting results: (1) exercise modalities: resistance versus aerobic exercise; (2) timing of exercise: intradialytic versus before dialysis session; (3) exercise intensity and duration; and (4) timing of blood collection: during HD versus before dialysis session. More research is needed in order to evaluate oxidative stress responses following acute exercise implemented at a wide range of exercise intensities in HD patients.

This study has some limitations. First, sample size is very small ($n=16$), and the results need to be confirmed in larger cohorts. Second, baseline levels of SOD and GPx are significantly different between the control and exercise group; this may be an important weakness of this study. Third, there was no significant difference in antioxidant enzymes except plasma SOD levels; the authors were not able to explain this finding clearly. Finally, they collected the data at 30 minutes and 60 minutes after starting the HD (before and after 30 minutes' exercise). HD itself may induce the change of the level of oxidative stress and antioxidant marker, thus the results can be affected by something other than intradialytic exercise.

In conclusion, although this report provides evidence that acute intradialytic exercise may have the potential to increase oxidative stress, several convincing data indicate that regular exercise decreases the incidence of oxidative stress-associated diseases as a result of exercise-induced adaptation. Chronic physical activity is associated with significant cardiovascular adaptations and reduced mortality risk in dialysis patients. However, these studies of exercise programs were undertaken in relatively healthy dialysis patients; therefore, these beneficial effects of physical exercise could not be extrapolated to all dialysis patients. Long-term clinical trials are needed to identify optimal modalities and doses of exercise for dialysis patients for a broad range of clinical outcomes.

Conflict of interest

The author declares no conflict of interest for this manuscript.

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