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REVIEW

Physical activity in chronic kidney disease and the EXerCise Introduction To Enhance trial

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ABSTRACT

It is well known from observational studies that sedentary lifestyle and reduced physical activity are common in dialysis and chronic kidney disease (CKD) patients and associate with an increased risk of morbidity and mortality in this patient population. Epidemiological studies indicate that CKD patients undergo physical activity ~9 days/month and 43.9% of dialysis patients report not exercising at all. On the basis of awareness about the strong link between sedentary lifestyle and adverse clinical outcomes, the National Kidney Foundation and Kidney Disease: Improving Global Outcomes have provided specific recommendations for physical activity in patients with kidney disease. Given the fact that CKD is a public health problem and it is still debated which type of exercise should be prescribed in these patients, this review focuses on the most robust evidence accumulated so far on the beneficial effect of various types of physical exercise on clinical outcomes in CKD and dialysis patients. This review does not treat this very important topic in another CKD category of patients, such as kidney-transplanted patients, for whom a special issue should be dedicated.

Keywords: chronic kidney disease, clinical trials, end-stage renal disease, physical exercise

INTRODUCTION

'Mens sana in corpore sano' is an old saying by Juvenal, a Roman poet, and it means that physical health goes together with mental health. Despite this, scientific evidence that physical exercise is beneficial for human health is much more recent and it was documented at Harvard University in the 20th century in a cohort of alumni enrolled between 1916 and 1950. In that large cohort of men, physical activity was documented to reduce the risk of coronary artery disease, and the interpretation of these findings was that physical activity is inversely related to the risk of coronary events. In addition to the Harvard University cohort, which was a sample of the general population, physical exercise has been associated with improvement in blood pressure (BP) and diabetes control and improved physical functioning. A strong inverse relationship between exercise and all-cause and cardiovascular mortality has also been reported both among healthy individuals and those with known cardiovascular disease. Furthermore, maintenance and improvement of physical fitness over time may also decrease the mortality risk. Despite the current recommendations, exercise rates in the general population remain low and the sedentary lifestyle is a growing and worrying risk factor in the third millennium. Indeed, lack of exercise is a major cause of chronic diseases and physical inactivity causes not only osteoporosis, degenerative joint disease and loss of neuromuscular strength, but also atherosclerosis, cardiovascular diseases and even cancer. Furthermore, physical inactivity has been documented to be associated with other growing issues such as Alzheimer's disease, dementia and depression. Among chronic disease epidemics that are responsible for most of today's worldwide death toll, chronic kidney disease (CKD) is one of the most burdensome for the national health systems worldwide. The National Kidney Foundation (NKF) and Kidney Disease: Improving Global Outcomes have developed physical activity recommendations for patients with renal disease that are similar to those for other chronic disease populations. Current recommendations include aerobic exercise 30 min on most days of the week. Observational and epidemiological studies have demonstrated that patients with CKD participate in physical activity ~9 days/month and 45% of patients with end-stage kidney disease (ESKD) [1] reported not exercising at all. These findings were attributed to various types of barriers and consistently differ between those barriers identified by doctors and those by patients themselves. Indeed, CKD is a public health problem, and although physical activity is considered essential for the prevention and treatment of most chronic diseases, exercise is rarely prescribed to patients with CKD. Of note, it is still to be debated (if indeed there is awareness of the need to discuss it) which type of exercise should be prescribed in this category of high-risk patients.

Physical activity in CKD patients not on dialysis

Among the modifiable lifestyle risk factors, physical inactivity is suspected to play a fundamental role in most chronic diseases. The issue is of particular relevance in CKD patients, a patient category in which substantially deteriorated fitness and frailty (one of the main consequences of physical inactivity) is strongly associated with adverse prognosis and reduced quality of life.

In a systematic review by Barcellos *et al.* [2] including 11 randomized controlled trials (RCTs) in pre-dialysis patients, the effect of various physical exercise programmes was assessed on a series of outcomes. In this article, among the three studies adopting inflammation as an endpoint, only the study by Castaneda *et al.* [3] found a positive effect of resistance training on circulating levels of C-reactive protein and interleukin-6. The same systematic review [2] also documented a beneficial effect of physical exercise on oxygen consumption (VO_2 peak, i.e. the maximum rate of oxygen consumption measured during incremental exercise) in five studies and on quality of life in two studies. These results are in keeping with those reported in a recent meta-analysis specifically focused on aerobic exercise training in adults with CKD [4], which documented that this intervention improved VO_2 peak and quality of life in CKD patients. Another study by Castaneda *et al.* [5] reported a beneficial effect of resistance training combined with a low-protein diet on the longitudinal changes of estimated glomerular filtration rate (eGFR) in CKD patients. In this latter study [4], over a short time period (12 weeks), eGFR increased in the resistance training group (+1.2 mL/min) and decreased in the control group (−1.6 mL/min) and the between-arms difference (2.8 mL/min) was statistically significant ($P = 0.048$). This result was confirmed in a recent meta-analysis by Zhang *et al.* [6], including 13 RCTs totaling 421 patients with CKD. In this meta-analysis, exercise therapy caused an increase in eGFR (+2.6 mL/min), which was of similar magnitude to that observed in the study of Castaneda *et al.* [5]. The article by Zhang *et al.* [6] also showed that patients in the exercise arm had a significant decrease in BP (systolic BP: −5.6 mmHg, diastolic BP: −2.9 mmHg) and body mass index (BMI, $-1.3\ kg/m^2$) as compared with controls but did not report a significant effect of the intervention on creatinine, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) in CKD patients.

Another interesting issue is whether a strong exercise programme associates with better clinical outcomes in CKD patients as compared with balance (i.e. less strength) physical exercise training. In an RCT (the RENEXC study) [7], the authors compared the effects of two different exercise programmes on physical performance, GFR [by iohexol clearance, measured GFR (mGFR)] and albuminuria in 151 patients with Stages 3–5 CKD randomly allocated to the balance group ($n = 75$) and the strength group ($n = 76$). Both groups were prescribed 30 min of exercise per day, 5 days/week, for 12 months. The prescribed exercises also comprised 60 min/week of endurance training and 90 min/week of either strength or balance exercises. In this trial, the effects on physical performance did not differ between the two study arms (strength versus balance training). However, a within-arm analysis showed that 12 months of regular strength or balance training combined with endurance training improved or maintained overall and muscular endurance and strength in patients with Stages 3–5 CKD. Of note, patients in the strength group had a significant decrease in albuminuria (−33%) as compared with those in the balance group, whereas the mGFR change was almost identical in the two arms ($P = 0.90$). Thus 12 months of either strength or balance training improved physical performance and might have beneficial effects on CKD progression. Unfortunately, the main limitation of the RENEXC study was that it did not include a sedentary control group.

Another RCT [8] investigated the effect of lifestyle intervention (i.e. access to multidisciplinary care through a nurse practitioner–led CKD clinic, exercise training and a lifestyle programme) versus usual care on metabolic equivalent tasks (METs), 6-min walking distance and other anthropometric measures in 72 patients with Stages 3 and 4 CKD [8]. The MET value was obtained from the treadmill based on the speed and inclines at the termination of the exercise stress test compared with sex-specific normative data. The exercise training was a two-phased programme in which patients received 8 weeks of supervised training before beginning 10 months of home-based training. Patients in the intervention arm showed a significant improvement in MET and 6-min walking distance as compared with those in the control group, whereas between-group changes in eGFR, BMI, urinary albumin:creatinine ratio and BP did not differ between them. Of note, 6-min walking distance increased (+11%) in the intervention group (baseline: 485 m, 12 months: 539 m), whereas it remained unchanged in the control group (baseline: 475 m, 12 months: 472 m; between-group difference, $P < 0.001$; Figure 1). The study also documented no serious adverse events related to the exercise programme. The effect of physical exercise as a potential strategy to lower BP in CKD was recently investigated in another systematic review including RCTs[9]. In this article, the authors examined the effect of exercise on BP control in adult Stages 3–5 CKD patients. Outcomes were non-ambulatory systolic BP (auscultation or oscillometric), 24-h ambulatory BP (ABPM) and two biomarkers of atherosclerosis and endothelial function such as pulse wave velocity and flow-mediated dilatation. Twelve studies with 505 participants were included. Ten trials (totaling 335 participants) reporting non-ambulatory systolic BP were meta-analysed. Exercise was associated with a significant lowering effect on non-ambulatory systolic BP in the short term (12–26 weeks) but not in the long term (48–52 weeks). In the two trials that measured BP by 24-h ABPM, the overall effect of exercise on systolic BP did not differ from that observed in controls. No effect of exercise was observed on pulse wave velocity and endothelial function.

Overall, exercise training may represent a potential strategy to improve eGFR and BMI in CKD patients. Limited evidence from short-term studies also suggests that exercise may reduce

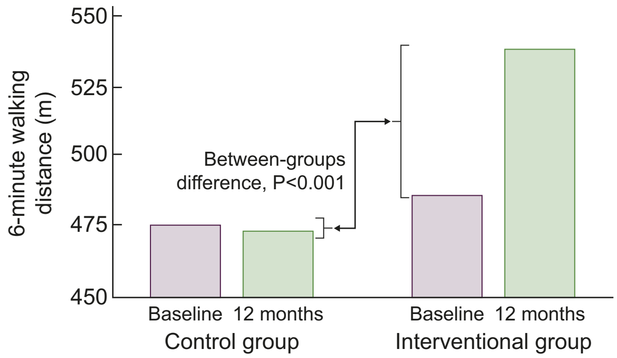

FIGURE 1: Effect of lifestyle intervention on the evolution over time of 6-min walking distance (redrawn from ref. [8]).

conventional BP (as measured by auscultation or oscillometric methods) but not 24-h ABPM or total, HDL or LDL cholesterol. RCTs on hard endpoints such as death and cardiovascular events have always focused on ESKD patients, while no attention at all has been reserved for non-dialysis CKD patients. In the near future, RCTs with larger sample sizes and long-term follow-ups are needed to better clarify the impact of exercise training on cardiovascular complications and CKD progression in this high-risk population. Physical activity should be investigated in CKD patients to assess whether the beneficial effect documented in the general population is also present in CKD patients. With sedentary lifestyle being a cardiovascular risk factor, a regular prescription of some degree of physical activity could be a treatment strategy for non-dialysis CKD patients that will have significant social benefits.

Physical activity in haemodialysis (HD) and peritoneal dialysis (PD) patients

ESKD patients on dialysis display an increased risk of morbidity and mortality, which is due in part to complications related to reduced physical function [10]. Several studies focused on the whole spectrum of CKD suggest a beneficial effect of exercise on physical performance and health endpoints [7, 11, 12]. To date, most systematic reviews and meta-analyses have included RCTs testing physical exercise programmes mainly as supervised training performed at the treatment centre, i.e. during inter- or intradialysis sessions [13, 14]. Overall, these trials documented an improvement in aerobic and walking capacity and in health-related quality of life in these patients, although, due to small-sized studies and differences in exercise modalities, intensity and duration, these results should be interpreted with caution. In a well-performed multicentre clinical trial enrolling 171 HD patients, a sustainable resistance exercise programme using elastic bands in a seated position during the first hour of HD treatment produced an objective improvement in physical function as assessed by the 30-s sit-to-stand (STS) and the 8-foot timed up and go (TUG) tests [15]. Remarkably, the observed outcome measures showed a significant increase in the number of 30-s STSs and a reduction in time for TUG after the exercise started, with no evidence of adverse exercise-related symptoms.

Despite these positive findings, different opinions still exist on how exercise training should be employed (in-centre or home-based) in the dialysis population. Since organization and cost problems associated with intradialytic modalities are difficult to overcome, home-based exercise needs to be progressively included in the training programme of dialysis centres to increase patient compliance and the feasibility of such interventions. Although potentially effective [12, 16], the literature on home-based training in the management of health-related endpoints of dialysis patients has not been fully defined. To date, a few RCTs have focused specifically on walking exercise programmes considering walking capacity as an outcome measure. Recently a review by Bohm *et al.* [17] identified relevant studies assessing the role of aerobic/resistance exercise on patient-reported outcomes, including for the first time a recent multicentre RCT testing a home, low-intensity walking exercise allowing a meaningful increase in walking distance and a significant improvement in cognitive and physical functions [12].

In contrast, the evidentiary basis for recommending exercise training in CKD Stage 5D is still limited and even when and how exercise training should be articulated (intradialysis or off-dialysis, in-centre only and daily versus other schedules) and implemented (duration and intensity) still remains an open problem. Therefore the main aim of this review is to focus not only on the importance of physical activity in HD patients but also to address the role of home-based exercise in these high-risk populations, reporting the main results of the EXerCise Introduction To Enhance performance in dialysis trial (EXCITE) [12]. This recently published RCT performed on HD and PD patients provided valid evidence about the effect of home-based exercise on physical fitness and health endpoints. Indeed, National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines formally recommend that all dialysis patients should be counselled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity and that physical functioning assessment and encouragement for participation in physical activity should be part of the routine patient care plan. To comply with these recommendations, an additional consideration that should be properly addressed is to assess the feasibility of such a prescription. In other words, exercise during the dialysis session is not easily affordable in the vast majority of dialysis centres worldwide. Another consideration is that dialysis session exercise programmes cannot be applied to PD patients, which are home dialysis patients by definition. All these considerations strongly stimulated the initiative to set up a trial testing home-based physical exercise programmes, which could be important not only to substantially enhance adherence but also to involve home dialysis patients, mainly PD patients and the most elderly. The question that was at the core of the EXCITE trial was whether low-intensity, home-based physical exercise could be of any benefit on physical performance and quality of life in dialysis patients. The issue was first explored in a preliminary pilot experience with a simplified programme of a home-based, individualized, low-intensity exercise programme in a small number of HD patients, and the main findings were so promising that a multicentre RCT, the EXCITE trial, was conceived and financially supported by the Italian Health System. In this trial, which is the first one on a particular topic such as exercise for dialysis patients performed at home, participant centres were located in several Italian regions. Because of the fact that this was a truly peculiar trial with a sizeable number of patients, it is of importance to describe it in full detail in this review. The aim of this study was to assess the clinical value of a 6-month, simple, personalized, home-based training period in dialysis (HD and PD patients). Exclusion criteria were very severe physical limitation (e.g. amputation and/or any other limitation to ambulation), clinical limitation, severe effort angina, Stage IV New York Heart Association (NYHA) heart failure, any intercurrent illness requiring hospitalization and a high degree of fitness (ability to walk a distance of >550 m in 6 min). Dialysis patients were randomly assigned to the active arm (exercise) and the control arm and all patients were stratified according to the NYHA classification. The performance tests in this trial were two very well-validated tests such as the 6-min walking test and the sit-to-stand (STS) test. The primary analysis, i.e. the major clinical endpoints, was the assessment of whether a 6-month home-based training intervention improves physical performance as measured by the 6-min walking test and the STS and quality of life [Kidney Disease Quality of Life (KDQOL), Rand Corporation, validated in Italian CKD patients]. The secondary outcomes included all-cause mortality. In addition to these outcomes, the safety of the exercise programme was assessed. The whole dialysis population cohort (the source population) consisted of 714 individuals. The number of eligible patients was 473, and among those, roughly 300 agreed to participate in the study and were randomized. Randomization was effective and at baseline the two groups (active arm and control arm) were highly comparable.

The distance covered during the 6-min walking test improved in the exercise group (mean distance ± SD: baseline, 328 ± 96 m; 6 months, 367 ± 113 m) but not in the control group (baseline, 321 ± 107 m; 6 months, 324 ± 116 m; P < 0.001 between groups). Similarly, the five times STST time improved in the exercise group (mean time ± SD: baseline, 20.5 ± 6.0 s; 6 months, 18.2 ± 5.7 s) but not in the control group (baseline, 20.9 ± 5.8 s; 6 months, 20.2 ± 6.4 s; P = 0.001 between groups). These results in a relatively large cohort of dialysis patients, the largest so far, indicate that some type of physical activity is beneficial in this high-risk population.

Another important endpoint in the EXCITE trial was quality of life, which was measured by the KDQOL Short Form (KDQOL-SF) and was performed using the version translated into Italian and specifically validated in a sample of the Italian population. It is well known that an important aspect in clinical research is the assessment of cognitive function, which is a broad term defined as 'an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves all aspects of perception, thinking, reasoning, and remembering'. Dialysis patients in the active arm of this trial showed a significant improvement in cognitive function, which is in part connected to social relationships. The cognitive function score in the kidney disease component of the KDQOL-SF improved significantly in patients in the exercise arm compared with those in the control arm (P = 0.04). Overall, the training programme was well tolerated and no major symptoms/complications during exercise were reported in the active arm of the trial. Of note, in an analysis restricted to patients who completed the trial (i.e. in a 'per protocol' analysis), the cumulative risk of hospitalization was lower [hazard ratio 0.46 (95% CI 0.22–0.97); P = 0.04] in patients in the active group than those in the control group (Figure 2). This finding was germane to another analysis of the EXCITE trial [18] testing the predictive value of the 6-min walking test *per se* (i.e. independently of the allocation arm) for death, cardiovascular events and hospitalization in the intention-to-treat population ($n = 296$ dialysis) of the trial. In multiple Cox models—adjusting for the allocation arms as well as for traditional and non-traditional risk factors—a 20-m increase in the 6-min walking test entailed a 6% reduction (P = 0.001) of the risk of the composite endpoint (i.e. mortality, fatal and non-fatal cardiovascular events and hospitalizations) and similar relationships existed between the same test with mortality (P < 0.001) and hospitalizations (P = 0.03) considered as single outcomes [18].

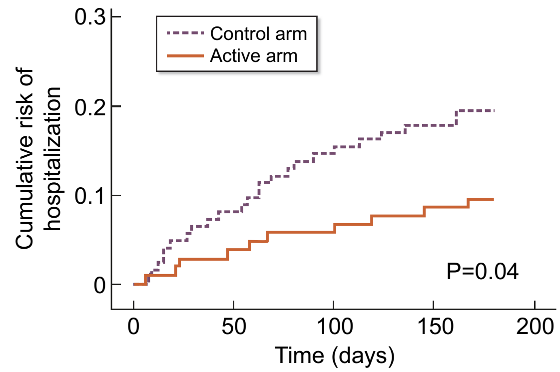

FIGURE 2: Reverse Kaplan–Meier survival curves for hospitalization in patients in the active group and those in the control group of the EXCITE trial (redrawn from ref. [12]).

Moreover, a secondary analysis of the EXCITE trial confirmed the beneficial effect of exercise on physical performance and cognitive function in dialysis patients >65 years of age [19]. Interestingly, an analysis of the EXCITE trial limited to PD patients (Mallamaci F. *et al.*, unpublished data) showed that the effect of physical exercise on the 6-min walk test in PD patients was identical to that observed in the whole study population. In contrast, the results for the STS test in PD patients were not different in the exercise group compared with the control group, but this could be due to the relatively small number of PD patients in the study.

In conclusion, so far the scientific community has dedicated a huge amount of effort to studying the burden of physical inactivity in dialysis patients [1], as well as the impact of physical exercise in the same patient population, but these programmes represent important barriers for their diffusion as routine treatment for the following reasons: (i) these programmes are conceived to be performed during dialysis sessions [20] and thus cannot be extended to the PD population, (ii) they are costly and (iii) they are not standardized and include too many types of exercise. The first trial that attempted to generalize (i.e. not performed during dialysis sessions) physical exercise in the dialysis population is the EXCITE trial. It generates the hypothesis that a simple, home-based, personalized exercise programme is well tolerated, improves physical performance and stabilizes cognitive function in dialysis patients. It should represent a stimulus to nephrologists for beginning long-term trials testing whether a simple exercise training plan can reduce the risk of many adverse health conditions and increase life expectancy and quality of life in a very high-risk population such as CKD patients, including patients with renal transplantation.

CONFLICT OF INTEREST STATEMENT

None declared.

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