

Exercise in Dialysis: Ready for Prime Time?

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Abstract

It is widely acknowledged that patients with end-stage kidney disease receiving maintenance hemodialysis (HD) may benefit from increasing their physical activity levels. Decades of exercise-related clinical trials have demonstrated improvements in various metrics related to dialysis patient's health and quality of life. Yet, the implementation of exercise programs in dialysis clinics today is scarce, and physical inactivity and dysfunction remain a hallmark of the disease. To address this issue, many groups worldwide are beginning to rethink how physical activity and exercise are prescribed in HD patients, as well as how to evaluate the efficacy of these programs. The vast majority of exercise interventions in HD patients have included intradialytic cycling as the predominant or only exercise prescription. Moreover, efficacy has most often been evaluated using standard measures of strength, physical function, and/or traditional cardiovascular disease risk factors (e.g., blood pressure, lipids, etc.). More recently, there has been a greater emphasis on novel intervention approaches that are focused on providing patients with a greater variety of options for exercise and enhanced motivational tools. The benefits of exercise on patient reported outcome measures (PROMs) and other clinically im-

portant outcomes are also becoming more prevalent. The purpose of this review was to: (1) critically review the data from several recently published large randomized clinical trials of exercise in HD patients, (2) discuss some of the novel approaches that groups across the world are taking to improve implementation and efficacy of exercise-related interventions in HD, and (3) discuss policy prescriptions that may be needed to continue improving exercise prescriptions for this critically ill patient population. While it may be too early to declare that exercise in dialysis is ready for prime time, exciting advances have been made in recent years, yet more work is needed to realize its full potential.

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Introduction

Exercise in Dialysis: Reasons for Concern

Many exercise interventions in dialysis patients have been published in recent decades, with most demonstrating some improvements in patient health and quality of life (QOL) [1]. Most of these studies have been in hemodialysis (HD) patients, and have utilized intradialytic cycling as the primary form of exercise, while a few have also included other mandated exercise prescriptions such as light resistance training and/or at-home walking programs [2]. While there is evidence to support that exercise

in HD patients can improve physical function, cardiovascular health, and QOL, the overall benefits seen in many of these studies are inconsistent or modest [3]. Moreover, much of the literature has been criticized for methodological concerns and other limitations in these studies, including small sample sizes, short intervention periods, and lack of control groups [1]. These perceived flaws may be contributing to the poor implementation of exercise programs in dialysis clinics globally.

Recently, several important RCTs and other studies have been published that address some of these limitations and improve our understanding of the benefits of exercise in dialysis patients. This includes several of the most robust intradialytic cycling trials published to date in terms of sample size and intervention duration [3–5]. While there were a number of design differences between these studies, each had similar disappointing results. For example, Koh et al. [4] conducted a 6-month RCT with 70 HD patients randomized to one of three groups: intradialytic exercise, home-based exercise, usual care. Patients in the intradialytic exercise group cycled for ~30 min at a moderate intensity, 3 times/week, for 6 months, while those in the home exercise group did a similar amount of walking exercise at home. Unfortunately, there were no significant improvements in objective measures of physical function (e.g., 6-min walk distance, timed-up-and-go [TUG], and grip strength) in either of the exercise groups compared to the control group, and self-reported physical function even decreased significantly in the intradialytic exercise group. There was also no observed change in blood pressure or arterial stiffness in the exercise groups compared to the controls. The IHOPE study by Jeong et al. [3] had similar disappointing results. This was an RCT in which patients were randomized to one of 3 groups for 12 months: (1) control; (2) oral protein supplementation (OPS; 30 g whey protein); or (3) OPS + intradialytic cycling (30–45 min, 3 days/week). Similar to the findings by Koh et al. [4], there were no improvements in physical function or arterial stiffness in the IHOPE trial. In another recent large RCT of intradialytic exercise titled the PEDAL study, Greenwood et al. [5] randomized 243 patients to a usual care/control group or intradialytic cycling for 12 months. The exercise group participated in intradialytic cycling 3 times/week, as well as performed intradialytic lower extremity resistance training 2 times/week. The exercise program was delivered and supervised by physiotherapy assistants. Unfortunately, neither health-related quality of life (primary outcome) nor physical function nor cardiovascular risk (secondary outcomes) improved significantly in the in-

tervention group relative to the controls. While the methods and intervention strategies in each of these studies [3–5] differed slightly, intradialytic cycling was a significant component of each intervention, and in each case, the primary and secondary outcomes related to physical function, cardiovascular health, and/or quality of life were not improved.

These results are disappointing, given that these are 3 of the largest and longest exercise related RCTs conducted to date in dialysis patients. Taken together, these data suggest that typical exercise prescriptions in dialysis patients may not be sufficient to produce consistent improvements in HD patients' health or quality of life. This may be due in part to the very low intensity and volume of exercise that is prescribed in these types of studies [1]. While most studies published to date have not included data related to exercise intensity or volume, those that have indicate that energy expenditure from a typical bout of intradialytic cycling may range between 15 and 75 kcal/session. Given the excessive burden of co-morbid disease, it is not surprising that dialysis patients have a difficult time completing a robust exercise intervention or that these modest exercise prescriptions sometimes provide disappointing results.

Reasons for Optimism

While the above-mentioned trials provide a pessimistic view of exercise in dialysis, a few other recent studies suggest reasons for optimism. This includes the recently published CYCLE trial, a robust ($N = 101$) RCT examining the efficacy of 6 months of intradialytic cycling on cardiovascular and physical function [6]. In contrast to the 3 studies described above [3–5], the CYCLE trial demonstrated that 6 months of intradialytic cycling *improved* cardiovascular structure and function, as measured by reductions in left ventricular mass and arterial stiffness. A primary difference in this study was that the cardiovascular changes were measured by MRI, which may provide more accurate assessments of changes in cardiovascular structure and function compared to cardiac ultrasound or arterial tonometry, which was used in most previous exercise interventions in HD patients. Unfortunately, similar to these previous studies, neither physical function nor QOL improved in CYCLE's exercise group compared to controls. However, the cardiovascular benefits demonstrated in this study are encouraging. Moreover, a secondary analysis of the CYCLE study showed there was a reduction in health care utilization costs by the exercise

group compared to controls, indicating the approach is potentially cost-effective [7].

Two recent pilot studies provided even more evidence of the novel cardiovascular benefits of intradialytic cycling. In both of these studies, an acute bout of intradialytic cycling significantly reduced myocardial stunning, compared to dialysis on days where exercise was not performed [8, 9]. This is an important finding given the potential deleterious consequences of dialysis-induced myocardial stunning in HD patients [10, 11]. Several recent studies have also demonstrated that intradialytic exercise improves a variety of patient-reported outcomes (PROs) in HD patients, including cramping, fatigue, and restless leg syndrome [12]. Taken together, these new studies indicate that exercise may have previously many unappreciated benefits on cardiovascular health and QOL, though more research is needed to confirm these intriguing findings.

What Is the Current State of Exercise in Dialysis Globally?

While less than 10% of dialysis centers globally offer exercise programs [1], there are several examples of robust programs in several countries, including Portugal, Germany, Mexico, and parts of Canada [13]. These programs each demonstrate that robust, sustained exercise programs are indeed feasible in HD clinics and can serve as a model for widespread implementation. For example, a dialysis provider in Portugal (Fresenius Medical Care/NephroCare) offers an intradialytic exercise program in most of their dialysis units across the country. The program was designed to be easy to learn for most of the patients and with low supervision from the dialysis staff and includes moderate intensity cycling and lower-limb strength exercises. Following a pilot phase in a single unit, the program was offered to all units. Unpublished data from the first year of its implementation showed that 21 out of 36 units adopted the program, and that in those units 56% of the patients were eligible to participate, whilst around 2/3 of those accepted to take part with an overall adherence to exercise of about 75%. Further, the program was safe and provided physical function improvements. However, within the first year, there was a 57% patient drop out, with about half of these patients opting out voluntarily.

Alberta, Canada embodies the “exercise is medicine” culture, providing support for CKD patients receiving home dialysis or in-center dialysis, and transplant pre-

rehabilitation and rehabilitation. This program is led by kinesiologists, medical staff, and students who educate patients with at-home exercises pertaining to strength, balance, and resistance training. Additionally, patients and their caregivers may attend weekly wellness classes to promote community support, share improvements, and manage the coping effects of their disease [13].

One HD unit in Mexico City, Mexico has implemented an intradialytic cycling program since 1994 that has since become a standard part of HD care for the past 25 years. All patients are mandated to exercise during dialysis, which includes participating in low-resistance cycling for 15 min every hour during treatment. While patient participation is high and the program is delivered by nephrology staff, the success of this program is in part due to the low number of patients at this particularly small clinic (~40 patients in total). One unique aspect of this program is that there is not designated financial support for the program. The bikes that are used are paid for out of general clinic funding, thus it is important to note that routine intradialytic exercise is feasible without large financial support [13].

Saxony, Germany also has a robust intradialytic exercise program that may serve as a model for other programs globally. The intervention approach used there consists of 30 min of endurance training and 30 min of resistance training delivered during dialysis by exercise specialists. What is unique about this program is the support of the program by a German health insurance company that covers the direct cost of the exercise program for patients. With this covered cost, patients exercising together during HD treatment, and the support from dialysis staff, motivation is high for patients in this program [13].

Other recent advances include the development of new guidelines for exercise in dialysis by various organizations around the world [14–16]. The Exercise and Sport Science of Australia (ESSA) published guidelines in 2013 that provided detailed recommendations for the prescription and delivery of aerobic and resistance exercise by trained professionals for patients with CKD [17]. In 2019, the Japanese Society of Renal Rehabilitation published clinical practice guidelines that have been implemented nationwide for non-dialysis CKD, dialysis patients, and transplant recipients [14]. Moreover, in April 2022, the Ministry of Health, Labor, and Welfare in Japan became the first in the world to extend rehabilitation coverage for IDE to HD patients by the National Health Insurance Reimbursement. In 2021, the UK Renal Association also published Clinical Practice Guidelines for Exercise and Life-

style in chronic kidney disease that reviewed the evidence base for exercise in CKD. Among other goals, the UK guidelines advocate for dialysis patients to participate in 150 min of aerobic and muscle-strengthening exercise per week [15]. Lastly, the International Society of Peritoneal Dialysis (ISPD) and Global Renal Exercise (GREX) Network recently published the first guidelines for exercise for peritoneal dialysis patients to help them maintain physical function and improve quality and quantity of life [16]. These new guidelines and other work done by these international organizations suggest that there is still a lot of enthusiasm for exercise in dialysis globally. Furthermore, these groups are demonstrating that widespread implementation is feasible and potentially cost-effective. So, what is holding exercise in dialysis back?

Barriers to Exercise in Dialysis and Policy Prescription for Implementation

Numerous barriers for exercise in dialysis patients have been identified. Primary patient-related barriers include fatigue, muscle cramping, poor physical function, depression, comorbid disease, and lack of motivation [18, 19]. The inability for nephrologists and dialysis staff to counsel and support patients exercising has also been described as a common barrier as well [20, 21]. While nephrologists overwhelmingly agree (~99%) that exercise is important for HD patients, less than 15% feel confident in their ability to counsel HD patients on the topic [21]. Furthermore, nephrologists have a skewed belief that patients do not want to exercise [21], when in fact, HD patients report they would like to, but lack the knowledge to do so [20].

There are also a number of policy barriers that need to be overcome to improve the implementation of exercise programs for dialysis patients. Details of these barriers and strategies to address them have been reviewed in detail previously [22], but include proposed changes to funding models, service provision, legislation, regulations, exercise guidelines, environmental factors, communication, and marketing strategies. For example, the CMS Quality Incentive Program provides reimbursements to dialysis facilities for performance metrics primarily related to biochemical indices. However, if reimbursement incentives were tied to quality of life metrics, this may incentivize lifestyle interventions like exercise programs. Additionally, the physical environment and social morale in dialysis clinics should be more inspiring and encouraging to patients, so as to promote physical

activity and a healthy lifestyle. Incorporating exercise equipment and designated space in renal clinics, as well as engaging in conversations about exercise and overall health, can foster an environment where exercise is effectively delivered to kidney disease patients [22]. Guidelines for implementation should include the delivery of exercise programs by trained exercise professionals. Exercise counseling remains low amongst nephrology staff, even with the majority belief that exercise and physical activity benefit patients [1]. Moreover, given that nephrology nurses and other healthcare providers have frequent interaction with patients, positive social interactions and the comprehensive incorporation of dialysis staff will increase the likelihood of success for patient physical-activity levels [18]. While encouragement of physical activity should be provided by all dialysis staff, intradialytic exercise should be primarily delivered by trained exercise professionals. Unfortunately, funding for this is limited in the USA and most other countries around the world.

Conclusion

Exercise in dialysis has come a long way in recent years, yet many questions remain. Regarding efficacy, while several recent large RCTs have shown disappointing results [3–5], others demonstrated previously unrecognized cardiovascular benefits [6, 8, 9] and improvements in patient reported outcomes such as fatigue, cramping, and restless leg syndrome [12]. And while implementation around the world remains low, several countries have intriguing exercise programs in dialysis clinics with widespread implementation [13]. This suggests that programs are feasible and likely cost effective [7]. A number of groups around the world are also considering more novel and comprehensive approaches to exercise as a way of improving compliance and feasibility. But a number of policy prescriptions are needed to enhance implementation, including, but not limited to, providing funding for trained exercise professionals to deliver exercise programs for dialysis patients. Until this happens, the potential for exercise to significantly improve the health and QOL of dialysis patients will remain unfulfilled.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ashley M. Morgan helped develop the outline, conducted the literature review, and composed the first draft of the manuscript. Kenneth R. Wilund helped develop the outline and provided revisions to the original draft. Alexis C. King and Joao Viana provided revisions to the original draft.

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