27. Black AP, Anjos JS, Cardozo L *et al*. Does low-protein diet influence the uremic toxin serum levels from the gut microbiota in nondialysis chronic kidney disease patients? *J Ren Nutr* 2018; 28: 208–214
28. Cotillard A, Kennedy SP, Kong LC *et al*. Dietary intervention impact on gut microbial gene richness. *Nature* 2013; 500: 585–588
29. Qin N, Yang F, Li A *et al*. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; 513: 59–64
30. Guida B, Germanò R, Trio R *et al*. Effect of short-term synbiotic treatment on plasma p-cresol levels in patients with chronic renal failure: a randomized clinical trial. *Nutr Metab Cardiovasc Dis* 2014; 24: 1043–1049
31. Rossi M, Johnson DW, Morrison M *et al*. Synbiotics easing renal failure by improving gut microbiology (SYNERGY): a randomized trial. *Clin J Am Soc Nephrol* 2016; 11: 223–231
32. Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008; 88: 660–666
33. Vaziri ND, Yuan J, Norris K. Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in chronic kidney disease. *Am J Nephrol* 2013; 37: 1–6

Received: 23.10.2018; Editorial decision: 20.5.2019

Nephrol Dial Transplant (2019) 34: 1816–1818

doi: 10.1093/ndt/gfz038

Advance Access publication 4 March 2019

Cardiovascular protection and mounting evidence for the benefits of intradialytic exercise

Allyson Hart and Kirsten L. Johansen

Division of Nephrology, Hennepin Healthcare System, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Correspondence and offprint requests to: Allyson Hart; E-mail: Hart1044@umn.edu

Although mortality has improved over the past few decades among patients on dialysis, rates remain significantly higher than those of the general population [1]. Given the ongoing shortage of organs for transplantation, additional interventions to improve mortality in the dialysis population are sorely needed. Cardiovascular disease in particular remains the leading cause of death, accounting for nearly 40% of deaths of patients on dialysis [1], making it a prime target for interventions to improve mortality in this population. Patients on dialysis also suffer from decreased physical function and quality of life [2, 3], and a recent study showed that patients with advanced chronic kidney disease (CKD) prioritize maintaining independence over staying alive [4]. Despite this priority, data on interventions to improve both mortality and patient function are lacking relative to the magnitude of the problem.

CARDIOVASCULAR DISEASE IN PATIENTS WITH ADVANCED CKD

The role of cardiovascular disease and dysfunction in the morbidity and mortality of patients with CKD is noncontroversial [5]. CKD confers increased cardiovascular risk beyond the traditional risk factors of hypertension and diabetes [5, 6], making cardiovascular disease a key target for interventions. However, clinical trials of interventions targeting atherosclerosis, such as the use of statins, have had disappointing results in dialysis patients, perhaps as a result of the higher prevalence of heart failure and sudden cardiac death than is observed among individuals with traditional atherosclerotic coronary disease [7]. In hemodialysis patients, in particular, disordered cardiovascular physiology during hemodialysis causes intradialytic hypotension

(IDH) and repeated cardiac ischemia, resulting in wall motion abnormalities and left ventricular dysfunction known as myocardial stunning [8–10]. Both IDH and myocardial stunning are associated with increased mortality [11–13], as well as important patient-centered outcomes such as post-dialysis fatigue [14, 15]. Efforts to mitigate these cardiovascular effects of dialysis have shown some promise, including cooled dialysate [16] and more frequent hemodialysis [17]. However, more frequent dialysis comes with additional costs, both in monetary terms and in terms of treatment burden, as extra treatments can be difficult for patients to tolerate or accept, resulting in poor adherence.

IMPACT OF EXERCISE ON CARDIOVASCULAR PHYSIOLOGY

Exercise has the exciting potential to be cardioprotective in dialysis patients. In the general population, exercise is associated with positive functional and structural physiological adaptations, including improved coronary artery vascular function, sympathetic nervous system function, coronary artery vascular structure and cardiac remodeling [18]. Acutely, exercise results in increased sympathetic activation resulting in increased heart rate and myocardial contractility. In addition, active skeletal muscle increases venous return, augmenting the left ventricular end-diastolic volume and contraction. Evidence in animals and humans suggests that exercise acutely attenuates cardiac ischemia [18]. These acute effects suggest that intradialytic exercise in particular, rather than an interdialytic outpatient exercise program, may have additional benefits for hemodialysis patients exposed to repeated ischemic episodes, beyond the long-term benefit one would expect from an exercise program (Figure 1).

FIGURE 1: Conceptual model of the possible beneficial cardiovascular effect of intradialytic exercise in dialysis patients.

IMPACT OF EXERCISE IN DIALYSIS PATIENTS

Studies evaluating the effects of exercise in patients on dialysis show improvements in many parameters, including exercise capacity, endothelial function, inflammatory markers, physical performance measures and health-related quality of life [19–22]. Interestingly, given its known cardiovascular benefits in the general population and the high prevalence of cardiovascular disease in dialysis patients, relatively little is known about the cardiovascular effects of exercise in this population. This is especially important because given the significant differences between the general population and patients on dialysis, particularly with regard to cardiovascular disease, caution must be exercised in extrapolating findings about the impact of exercise in the general population to patients on dialysis. In addition, dialysis patients have markedly decreased exercise capacity at baseline [19]. Although several small studies evaluating the hemodynamic effects of intradialytic exercise have shown the expected physiologic responses, there are limited data about the cardiovascular effects, particularly on myocardial perfusion [14]. The available hemodynamic data support the possibility that intradialytic exercise could increase myocardial perfusion and decrease myocardial stunning, but additional data are needed to determine first its cardiovascular effects and ultimately its impact on mortality and other patient-centered endpoints, such as the post-dialysis fatigue associated with myocardial stunning.

In addition, exercise is not without risk. In addition to the potential for musculoskeletal injury, dialysis patients are at higher risk for dysrhythmia and cardiac ischemia, which could be exacerbated further by the fluid and electrolyte shifts that occur during dialysis. Clinicians have raised concern that intradialytic exercise could worsen IDH and lead to cardiac ischemia or decreased splanchnic blood flow and bowel ischemia and fear that these risks may mitigate the enthusiasm for intradialytic exercise. However, studies of both intradialytic and ambulatory exercise programs have supported the safety of this intervention when employed with best practices of a warm-up period, starting at low intensity and avoiding high-impact activities [14, 19]. Further evaluation of the risk–benefit ratio of intradialytic exercise is warranted.

INTRADIALYTIC EXERCISE AND MYOCARDIAL STUNNING

In this issue, Penny *et al.* [23] report on the effect of intradialytic exercise on myocardial stunning. Participants of this study were already participating in the Manitoba Renal Program’s Intradialytic Exercise Program, a voluntary regimen of stationary cycling for 30–60 min at a moderate subjective intensity during the first half of their dialysis treatment under the supervision of a kinesiologist. Echocardiography was performed on 19 patients during a dialysis session with (control) and without exercise. Investigators evaluated the difference in regional wall motion abnormalities at peak stress (15 min prior to the end of dialysis treatment) as the primary outcome, as well as the number of intradialytic hypotensive episodes, concluding that intradialytic exercise was associated with less myocardial stunning with no difference in the incidence of IDH.

This small exploratory study is nonrandomized and subject to selection bias; subjects were prevalent patients in the exercise program, having been approved for the program by their nephrologists, with frequent IDH serving as a relative contraindication and having tolerated routine exercise participation prior to the sessions during which echocardiography was performed. However, the study provides sound evidence to justify further exploration in a longitudinal randomized trial to evaluate whether these echocardiographic findings translate to cardiovascular event and survival benefits, as well as improvement in patient-centered outcomes such as functional status and post-dialysis fatigue. In particular, given the lack of interventions found to improve rates of sudden cardiac death in dialysis patients, evaluation of how attenuation of intradialytic cardiac ischemia related to intradialytic exercise affects this cardiovascular outcome is warranted.

EVALUATING THE IMPACT OF EXERCISE ON PATIENT-CENTERED OUTCOMES

This study also adds to a growing body of evidence supporting exercise interventions in dialysis patients for a myriad of benefits beyond survival and cardiovascular events. An intervention that has the potential to impact multiple domains of health, including symptoms, functionality and independence, deserves additional exploration. Patient-centered outcomes have often been sidelined in the search to improve survival in dialysis patients. However, efforts to elevate the awareness of patient-centered outcomes in addition to mortality have gained momentum. Extensive work by Tong [24, 25] and others to synthesize patient and provider input to develop core outcome measures are helping to frame nephrology research to include patient-centered outcomes. The importance of this work was again highlighted recently by Ramer *et al.* [4], who surveyed patients with advanced CKD and found that most prioritized independence over survival. Importantly, this study also found that nephrologists’ ability to predict these patient’s priorities was limited.

ADDRESSING BARRIERS TO INTRADIALYTIC EXERCISE

In addition to facing uncertainty about the ideal ‘dose’ and type of exercise to achieve targeted benefits, most nephrologists

currently lack the tools and resources needed to fully support exercise programs for their dialysis patients. Competing demands and patient needs make the inclusion of an exercise program challenging, and dialysis patients are heterogeneous in functional capacity and comorbidities. In reviewing approaches to sustaining a dialysis exercise program, Capitanini *et al.* [26] outline structural, cultural, financial and clinical barriers that dialysis providers and patients currently face. They offer three critical elements of a successful program, including involving an exercise professional, obtaining full buy-in from dialysis clinic professionals and adapting the exercise program to the individual patient. Dialysis care already provides a model for the implementation of these solutions. The nephrology community has embraced a multidisciplinary care model for these complex patients, recognizing that no one individual has all of the expertise or ability necessary for dialysis patients to thrive. However, resources are not routinely available to support exercise professionals as part of the multidisciplinary team.

Policy remains an important driver for the implementation of innovative care models. Performance measures set by quality incentive programs result in the allocation of resources and attention to the quality metrics that are tied to reimbursement rates. These quality metrics currently include no measures of patient function or quality of life. The addition of incentives, such as quality metrics that prioritize and reward patient function and quality of life, may help overcome the activation energy required to incorporate exercise counseling into the routine care of dialysis patients. Studies such as this one by Penny *et al.* [23] are an early but welcome step in generating data to support the benefits of a more holistic dialysis patient care model.

FUNDING

Support for this work was provided by the National Institute of Diabetes and Digestive and Kidney Diseases Award numbers R01-DK107269 and K24-DK-085153.

CONFLICT OF INTEREST STATEMENT

None declared. This article has not been published elsewhere in whole or in part.

(See related article by Penny *et al.* Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning. *Nephrol Dial Transplant* 2019; 34: xxx-xxx)

REFERENCES

1. United States Renal Data System. 2017 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases, 2017
2. Spiegel BM, Melmed G, Robbins S *et al.* Biomarkers and health-related quality of life in end-stage renal disease: a systematic review. *Clin J Am Soc Nephrol* 2008; 3: 1759–1768
3. Bao Y, Dalrymple L, Chertow GM *et al.* Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 2012; 172: 1071–1077
4. Ramer SJ, McCall NN, Robinson-Cohen C *et al.* Health outcome priorities of older adults with advanced CKD and concordance with their nephrology providers' perceptions. *J Am Soc Nephrol* 2018; 29: 2870–2878
5. Herzog CA, Asinger RW, Berger AK *et al.* Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; 80: 572–586
6. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32(5 Suppl 3): S112–S119
7. Cheung AK, Sarnak MJ, Yan G *et al.* Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. *Kidney Int* 2004; 65: 2380–2389
8. Burton JO, Jefferies HJ, Selby NM *et al.* Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol* 2009; 4: 1925–1931
9. Burton JO, Korsheed S, Grundy BJ *et al.* Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmias. *Ren Fail* 2008; 30: 701–709
10. McIntyre CW, Burton JO, Selby NM *et al.* Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol* 2008; 3: 19–26
11. Flythe JE, Xue H, Lynch KE *et al.* Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol* 2015; 26: 724–734
12. Shoji T, Tsubakihara Y, Fujii M *et al.* Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int* 2004; 66: 1212–1220
13. Tisler A, Akocsi K, Borbas B *et al.* The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant* 2003; 18: 2601–2605
14. McGuire S, Horton EJ, Renshaw D *et al.* Hemodynamic instability during dialysis: the potential role of intradialytic exercise. *Biomed Res Int* 2018; 2018: 8276912
15. Dubin RF, Teerlink JR, Schiller NB *et al.* Association of segmental wall motion abnormalities occurring during hemodialysis with post-dialysis fatigue. *Nephrol Dial Transplant* 2013; 28: 2580–2585
16. Odudu A, Eldehni MT, McCann GP *et al.* Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients. *Clin J Am Soc Nephrol* 2015; 10: 1408–1417
17. Jefferies HJ, Virk B, Schiller B *et al.* Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol* 2011; 6: 1326–1332
18. Thijssen DHJ, Redington A, George KP *et al.* Association of exercise preconditioning with immediate cardioprotection. *JAMA Cardiol* 2018; 3: 169–176
19. Johansen KL. Exercise and dialysis. *Hemodial Int* 2008; 12: 290–300
20. Ouzouni S, Kouidi E, Sioulis A *et al.* Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients. *Clin Rehabil* 2009; 23: 53–63
21. Sakkas GK, Hadjigeorgiou GM, Karatzafiri C *et al.* Intradialytic aerobic exercise training ameliorates symptoms of restless legs syndrome and improves functional capacity in patients on hemodialysis: a pilot study. *ASAIO J* 2008; 54: 185–190
22. Manfredini F, Mallamaci F, D'Arrigo G *et al.* Exercise in patients on dialysis: a multicenter, randomized clinical trial. *J Am Soc Nephrol* 2017; 28: 1259–1268
23. Penny JD, Salerno FR, Brar R *et al.* Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning. *Nephrol Dial Transplant* 2019; 34:1917–1923
24. Tong A, Manns B, Hemmelgarn B *et al.* Establishing core outcome domains in hemodialysis: report of the Standardized Outcomes in Nephrology-Hemodialysis (SONG-HD) Consensus Workshop. *Am J Kidney Dis* 2017; 69: 97–107
25. Tong A, Manns B, Hemmelgarn B *et al.* Standardised outcomes in nephrology-haemodialysis (SONG-HD): study protocol for establishing a core outcome set in haemodialysis. *Trials* 2015; 16: 364
26. Capitanini A, Lange S, D'Alessandro C *et al.* Dialysis exercise team: the way to sustain exercise programs in hemodialysis patients. *Kidney Blood Press Res* 2014; 39: 129–133

Received: 24.1.2019; Editorial decision: 25.1.2019