The cardiovascular adaptations associated with exercise in patients on haemodialysis

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Abstract

Patients on haemodialysis are physically inactive. Less than 50% of haemodialysis patients undertake exercise once a week and such patients have increased mortality compared to patients who undertake regular exercise. The reasons for physical inactivity and reduced functional capacity are complex and inter-related, with Skeletal muscle catabolism, chronic inflammation, anaemia, malnutrition, uraemia, the burden of co-morbid diseases and 'enforced' sedentary time during haemodialysis all contributing. Many of these factors drive cardiovascular disease processes in this population and in the general population, exercise interventions have been shown to modify many of these risk factors. Whilst there increasing data on the effects of exercise interventions on quality of life, functional capacity, aerobic fitness and muscular strength, there are few compelling data on the effects of such programmes on cardiovascular outcome measures. The reasons for this are manifold, and include limitations in study size, inconsistencies in study design, the herterogeneous nature of exercise interventions, assessment of non-standardised outcome measures and a lack of understanding of what changes in certain traditional measures of cardiovascular disease (such as blood pressure or lipid profile) mean for patients on haemodialysis. This review summarises the current evidence base for the effects of exercise on traditional and non-traditional cardiovascular risk factors and the effects of exercise interventions on cardiovascular structure and function, including a review of study limitations and future research priorities.

Introduction

United States renal data system (USRDS) data suggests that cardiovascular disease (CVD) is the leading cause of death in haemodialysis patients, accounting for 42.3% of all deaths (1). These excessive rates of CVD are multifactorial and explained by clustering of risk-factors, which may be considered 'traditional' or 'non-traditional'. 'Traditional' risk-factors for CVD include age, hypertension or dyslipidaemia and drive classical coronary artery disease related morbidity and mortality in the general population (2). Traditional risk-factors alone do not explain the excess cardiovascular morbidity and mortality in haemodialysis patients (3) and strategies to improve CVD-related outcomes, such as coronary revascularization, have not improved outcomes for patients with end stage renal disease (ESRD) in the same way as they have in the general population (4). 'Non-traditional' risk-factors are related to the unique environment encountered in ESRD and include uraemia, endothelial-dysfunction, bone-mineral metabolism abnormalities, anaemia, volume-overload, systemic inflammation and haemodialysis itself (5-8). These non-traditional risk-factors lead to pathological changes in cardiovascular structure and function including left ventricular (LV) hypertrophy (LVH); stiffening of the major arterial trunk; LV dilatation; and non-coronary artery disease-related myocardial fibrosis (9-12). These pathological changes in structure and function account for much of the excessive rates of CVD and sudden cardiac death in patients with ESRD and interventions are needed that address both traditional and non-traditional risk factors for CVD in these patients.

Patients on haemodialysis are physically less active than even sedentary patients, with <50% of haemodialysis patients reporting exercising once a week, with associated higher mortality (13). Skeletal muscle catabolism, chronic inflammation, anaemia, malnutrition, uraemia, the burden of co-morbid diseases and 'enforced' sedentary time during haemodialysis all contribute to these poor levels of functional capacity and exercise capabilities (13, 14), and these, in turn, associate with disability, decreased survival (15), increased use of healthcare (16) and reductions in quality of life (17). Reduced physical activity levels have been shown to associate with markers of inflammation, nutrition and muscle-wasting (18, 19) and a variety of exercise regimens have been shown to moderate key non-traditional risk factors that drive CVD in patients with chronic kidney disease (CKD) and ESRD, including systemic inflammation, endothelial dysfunction and reversing the catabolic state and protein muscle-wasting (20-24). Epidemiological studies have even suggested that the relative risk of mortality is lower in dialysis patients who participate regularly in exercise (25) but there are few clinical studies that have properly assessed the effects of exercise on cardiovascular disease and cardiovascular outcomes in patients on haemodialysis. In this review we will discuss how exercise may be delivered to patients on haemodialysis and review the literature that has assessed the effects of exercise on aspects of CVD in patients on haemodialysis, as well as the gaps in the evidence.

Types of exercise for patients on haemodialysis

Several small studies have assessed the impact of a variety of exercise interventions on CVD in patients on haemodialysis. There are no studies that have been sufficiently large to estimate effects on mortality, and all possible beneficial effects are based on surrogate markers of CVD. Broadly speaking studies that have assessed the effects of exercise in patients on haemodialysis patients have delivered an exercise intervention in one of two ways (table 1):

1. Intra-dialytic exercise, which is undertaken during dialysis sessions. Intra-dialytic exercise programmes tend to have better adherence rates, but poorer cardio-respiratory adaptations (26). This is often in the form of intra-dialytic cycling via a modified cycle ergometer (IDC).
2. Inter-dialytic exercise, which take place between dialysis sessions on non-dialysis days. These programmes tend to lead to greater cardio-respiratory improvements but have higher drop-out rates (27).

Similarly the exercise undertaken can be divided in to (table 1):

1. Aerobic training exercise, which improves aerobic threshold and maximal oxygen usage.
2. And resistance training, which focuses on strengthening particular muscle groups through weights/resistance bands, often with flexibility and core stability exercises.

Certain studies have implemented combined aerobic and resistance exercise programmes, as well as studies which have assessed the effects of exercise programmes in combination with lifestyle or dietary interventions. In health and disease states, aerobic and resistance exercise training have distinct physiological effects, so an appreciation of these differences is essential when interpreting cardiorespiratory adaptations to exercise programmes in haemodialysis patients.

Effects of exercise on blood pressure

The relationship between blood pressure and outcome in dialysis patients is 'U'-shaped (28). Whilst high blood pressure associates with mortality, low blood pressure associates even more strongly with mortality, (29) and due to the absence of trial data, firm guidelines for optimal management of blood pressure for patients on haemodialysis are not possible. The putative effects of exercise on blood pressure in patients on haemodialysis must, therefore, be interpreted with this in mind.

A non-randomised controlled study of 75 haemodialysis maintenance patients by Miller et al showed that IDC had no significant effect on pre or post-dialysis BP, although there was a significant reduction in the number of BP medications in patients in the exercise group (30). A subsequent cohort study of 19 haemodialysis patients by Anderson et al suggested that 3-6 months IDC led to a significant reduction in ambulatory BP, although similarly showed no changes in pre-and post-dialysis blood pressure, or changes in numbers of medicaitons (31). A cohort study of 11 patients by Mustata et al suggested that not only did 3 months of IDC training lead systolic BP and pulse pressure, but that these changes reverted to their previous baseline once cycling was discontinued (32). Furthermore, reductions in pulse pressure correlated with significant reductions in arterial stiffness (measured using radial artery pressure waveform analysis), which also reverted to baseline following the discontinuation of exercising, offering some mechanistic insight into ways BP may be moderated by exercise. A randomised cross-over study by Dungey et al showed that whilst BP increases during IDC, there is a resultant period of asymptomatic hypotension in the hour following exercise (33). This is a potential concern as episodes of intra-dialytic hypotension are a poor prognostic sign and strongly linked to adverse outcomes (8, 34). However in the paper by Dungey et al, there were no associated changes in humoral markers of cardiac disease or systemic inflammation (including hsTroponin I, IL-6 or TNF-α). Indeed a recent non-randomised study of IDC and resistance training by Rhee et al showed exercising during dialysis resulted in a reduction in episodes of symptomatic hypotentsion (35). The reduction in BP following exercise described by Dungey et al was asymptomatic and could simply reflect a normal, benign, physiological response to exercise, but future studies should be aware of this phenomenon to ensure sufficient safety can be built-into trial design. Improvements in both systolic and diastolic BP (measured by 24-hour ambulatory BP monitoring) were demonstrated by a randomised controlled trial of 50 patients on haemodialysis undertaking inter-dialytic aerobic and resistance training (36), although a larger study by Manfredini et al found that six-months home-based walking exercise had no significant effect on blood pressure, although this study included haemodialysis (n=192) and peritoneal dialysis patients (n=35). A 2014 systematic review by Sheng et al concluded that it is likely that intradialytic exercise programmes have a positive effect on BP (37), but Interestingly, a recent systematic review and meta-analysis by our group that looked exclusively at randomised controlled trials of IDC found there is insufficient randomised controlled data to conclusively say whether programmes of IDC improve BP control in haemodialysis patients (38). Safe to say, the data surrounding the effects of exercise on blood pressure are inconclusive. This is partly because there is no 'ideal' blood pressure for patients on dialysis, so it is difficult to know what constitutes an improvement on a population level. Rather than simply reporting the effects of exercise on blood pressure, future large studies (particularly randomised controlled trials) should report the effects of programmes of exercise in patients with documented hypertension, for whom a reduction in blood pressure is likely to be beneficial.

Effects of exercise on traditional and non-traditional cardiovascular risk factors

In the general population, exercise interventions are known to impact positively on traditional cardiometabolic risk factors, including cholesterol and triglyceride levels (39-41). Several small studies have reported the effects of exercise on these traditional risk factors, but given that traditional risk factors do not explain the excess cardiovascular morbidity and mortality in patients on haemodialysis, the relative importance on possible reductions in these variables needs to be questioned. Small, non-controlled studies of inter and intradialytic aerobic training have suggested that structured programmes of exercise improve triglyceride control and promote favourable alterations in lipid profile (36, 42, 43). Supporting this a pilot randomised trial by Wilund et al suggested that IDC led to a reduction in the atherogenic index of plasma and epicardial fat thickness (proposed as a determinant of CVD and implicated in pathogenesis (44)) (23). Of perhaps more interest are the studies that have assessed the effects of exercise on non-traditional risk factors for cardiovascular disease in patients on haemodialysis, particularly measures of vascular and systemic inflammation, which are heavily implicated in the pathogenesis of cardiovascular disease in patients on haemodialysis (45-47). A randomised control trial by Cheema et al, showed that a 12-week programme of progressive resistance training during dialysis reduces levels of systemic inflammation, with patients in the exercise group having significant reductions in C-reactive protein compared to controls (48). These findings are corroborated by a randomised controlled trial by Liao et al who demonstrated that a 3-month programme of intradialytic cycling may lead to reductions C-reactive protein and circulating Il-6 (49). Importantly this finding was on a 'change from baseline' analysis in the cycling group and not a between group comparison. The same study, however, did show that the 3-months intra-dialytic cycling programme led to increased numbers of circulating endothelial progenitor cells, which are a measure of endothelial repair and indicate an improvement in endothelial function, though again this finding was on a 'change from baseline' analysis rather than a between group analysis. A smaller randomised study by Manfredini et al showed that a home-based walking exercise may have similar effects. Patients who completed a 6-month programme of walking exercise were shown to have significant improvements in circulating endothelial colony forming units (another surrogate of endothelial function) (50). The same study showed no change in numbers of endothelial progenitor cells however. Some studies have reported a neutral effect of exercise on measures of systemic inflammation in patients on haemodialysis undertaking exercise. Dungey et al showed that inta-dialytic cycling did not affect the amount or profile of circulating pro-inflammatory cytokines or neutrophil function immediately after exercise (33). In a follow-up study the same group confirmed that intradialytic cycling did not affect levels of circulating pro-inflammatory cytokines, but it did have a positive effect on inflammatory cell profile, with patients undertaking exercise having significant reductions in numbers of intermediate monocytes and patients not undertaking exercise having significant reductions in numbers of regulatory T-cells (24). A small non-randomised controlled study by Wong et al showed that intra-dialytic exercise had no effect on circulating levels of endotoxin compared to control patients, but may promote a reduction in levels of circulating pro-inflammatory cytokines over time (51). The amelioration in pro-inflammatory cytokine profile is almost certainly mediated at a cellular level. Indeed, a recent study by Abreu et al showed that 3-months inter-dialytic resistance training in haemodialysis patients increases expression of anti-nuclear factor erythroid 2-related factor 2 (Nrf2); a nuclear transcription factor that is responsible for upregulating transcription of genes which encode phase II detoxification and antioxidant enzymes (52).

There is no strong data to suggest exercise improves the lipid profiles of patients on haemodialysis. Whether small reductions in lipid profile would result in meaningful improvements in mortality for these patients is highly speculative given the role of lipids in the pathogenesis of cardiovascular disease in patients on dialysis and the neutral effects of statin/fibrate therapy (53). There are more and better, though still conflicting, data on the effects of exercise on measures of systemic and vascular inflammation in patients on haemodialysis. Exercise may improve the pro-inflammatory cytokine profile associated with ESRD, may improve measures of endothelial function and may improve the inflammatory cell profile, but all of these findings need confirmation in large, adequately powered randomised controlled trials. Importantly there are currently no longitudinal data linking reductions in levels of systemic inflammation related to exercise to hard outcomes such as mortality or major cardiovascular events in patients on haemodialysis.

Effects of exercise on cardiovascular structure and function

For patients on haemodialysis, pathological changes in cardiovascular structure and function associate strongly with outcome (54-56) and LV function and LVH and measures of aortic stiffness have been used extensively in clinical studies of surrogates of outcome in interventional trials. Several studies have assessed the effects of exercise during dialysis on LV mass and LV ejection fraction (LVEF). A randomised controlled study by Kouidi et al suggested that improvements in aerobic capacity (VO2 peak) following a structured programme of intradialytic exercise associated with improvements in LVEF compared to control patients, but with no change in LV mass (57). Similarly a small randomised controlled study by Momeni et al, suggested that 3 months of 30 minutes IDC resulted in improvements in LVEF, reductions in pulmonary artery size and right ventricular size, with no changes in LV mass between exercise and control groups (58). Similarly an older randomised controlled trial of moderate, home-based exercise and intense, supervised interdialytic exercise showed that both programmes were associated with improvements in LVEF and stroke volume index compared to controls, although they also reported a small increase in LV mass in both exercising groups (59). Importantly all these studies used echocardiography to assess LV structure and function. Whilst echocardiography is an important tool for clinical use there are important limitations to it's use in patients prone to fluid overload (such as patients on dialysis) that mean both LV mass LV end-diastolic volume may be significantly overestimated in patients on haemodialysis (60). When imaged with 2D-ECHO LV mass and cavity size may be overestimated in up to 50% of dialysis patients when directly compared to LV mass measured by cardiac magnetic resonance imaging (CMR) (61). Studies comparing the reproducibility of LV mass, LVEF and LV dimensions using echocardiography and cardiac MRI would suggest that all of the studies to date that have assessed changes in LV geometry with echocardiography are dramatically under-powered to confidently detect a difference between groups (62). Additionally, whilst the above studies suggest exercise may improve LVEF in patients on haemodialysis, a systematic review and meta-analysis by our group that included only randomised controlled trials of patients undertaking intra-dialytic cycling found no effect of exercise on LVEF (38). Again though, this could be down to statistical power and based on the current evidence base, no firm conclusions can be made on the effects of exercise on LV structure and function in patients on haemodialysis.

Arterial stiffness, (particularly aortic stiffness) predicts cardiovascular outcomes in a similar way to LV mass (56), and the effects of exercise on aortic and peripheral pulse wave velocity have been assessed in several studies of patients on haemodialysis. Mihaescu et al showed in a non-randomised controlled trial that 40 minutes of intra-dialytic exercise associated with reduction in aortic pulse wave velocity compared to control subjects (63). A prospective cross-over study of 19 patients by Toussaint et al suggested exercise not only associated with improvement in pulse wave velocity, in patients undergoing exercise, but that the effects were lost after 3 months of not exercising suggesting any putative benefit may require exercise to be ongoing to derive benefit (64). However, the analyses undertaken in this study were changes from base-line, rather than between group comparisons, limiting the significance of this small study. The largest study to assess the effects of exercise on arterial stiffness was conducted by Koh et al. This pilot randomised controlled trial compared the effects of intra-dialytic exercise to home-based exercise and to control subjects and found the exercise interventions had no significant effect peripheral arterial stiffness measured compared to control subjects (65). Whilst it could be argued that the prognostic relevance of peripheral arterial stiffness is limited when compared to aortic pulse wave velocity and negative result in this study could simply be due to statistical power, the study by Koh et al was rigorously performed and reported.

Conclusions

It is logical that exercise training should be good for patients on haemodialysis, and there are good data showing exercise training improves muscular strength and quality of life (22). The empirical data for the beneficial effects of exercise on aspects of cardiovascular disease implicated in disease processes specific to patients with advanced renal failure, at this stage, are less compelling. This is partly because the studies are small and sometimes with a non-randomised design, but also because the way outcome measures are assessed and reported have not been standardised, limiting the ability to synthesise the available data. Two large randomised controlled trials will report over the next year or so which should significantly improve our understanding of the effects of intra-dialytic exercise on cardiovascular disease in patients on haemodialysis. The PEDAL study (NCT02222402) is a multi-centre randomised controlled trial that will assess the effects of nine months intra-dialytic exercise on quality of life, with a number of pre-defined cardiovascular secondary end-points. Similarly the CYCLE-HD study is a cluster-randomised controlled trial assessing the effect of intra-dialytic cycling on LV structure and function assessed with cardiac MRI (66) (ISRCTN11299707). The CYCLE-HD study is powered to detect a 15g difference in LV mass between groups over the study period and will assess the effects of exercise on a number of other pre-defined cardiovascular end-points, including measures of aortic stiffness and diastolic dysfunction assessed by cardiac MRI.

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Tables

Table 1: Advantages and disadvantages of different exercise training programmes for patients on haemodialysis

	Advantages	**Disadvantages**
Intra-dialytic exercise	• Superior adherence rates to exercise programme • Convenient for patients, making use of otherwise sedentary-time • Delivery supervised by physiotherapists and nursing staff	• Reduced cardiovascular adaptations compared to inter-dialytic programmes • Potentially may not be suitable for patients at risk of demand ischaemia on dialysis (frequent intra-dialytic hypotension) • Limited number of exercises that can be undertaken
Inter-dialytic exercise	• Superior cardiovascular adaptations compared to intra-dialytic programmes • Potential to undertake a greater range of exercise interventions	• Higher dropout rates from programmes compared to intra-dialytic exercise programmes • Conducted in otherwise 'free time' on non-dialysis days and may impact on time available to work, to fulfil activities of daily living or be with family
Aerobic training	• Improves aerobic threshold • Improves maximal oxygen usage	• Limited improvements in muscular strength and endurance • More limited improvements in functional capacity
Resistance training	• Improves physical strength • Improves functional capacity	• Limited improvements in aerobic capacity