Frequent Hemodialysis: A Way to Improve Physical Function?

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Whether using quantified tests to assess physical capabilities, or via validated questionnaires, physical function is notably reduced in chronic hemodialysis patients (1). Physical function is a major component of quality-of-life assessment in this population (2) and is best defined as an individual’s ability to perform activities in their daily lives (ADLs) (3). Notably, both poor physical performance and low self-reported physical function scores are predictive of future hospitalization and mortality in chronic hemodialysis patients (4–7). Increased solute removal during hemodialysis has been proposed as a mechanism to reduce mortality, as Kt/urea (the product of the urea clearance and the duration of the dialysis session normalized to the volume of distribution of urea) correlates directly with survival (8). The Hemodialysis (HEMO) study examined the effects of more intense hemodialysis sessions on mortality. Although the intervention failed to demonstrate a survival benefit (9), self-reported physical function was modestly improved (10). In the Frequent Hemodialysis Network (FHN) trial, frequency of hemodialysis was increased (to six times per week) to boost solute removal, again hypothesizing that mortality may be reduced (8). As secondary outcomes, the FHN trial assessed the effect of frequent hemodialysis on physical performance, health, and functioning. The results are presented in this issue of CJAASN by Hall et al. (11).

Hall and colleagues demonstrated that, compared with conventional hemodialysis, frequent daily hemodialysis improved the physical health composite (PHC) score, a measure of self-reported physical function. The physical functioning (PF) subscale, also a measure of self-reported physical function but without the inclusion of ratings for general health, bodily pain, and readiness for everyday physical activities, trended toward improvement as well (although the magnitude of change was large, it failed to reach statistical significance). In contrast, the short physical performance battery (SPPB) score, which quantitatively evaluates the ability to perform basic physical activities, was unchanged. Unlike frequent daily hemodialysis, frequent nocturnal hemodialysis did not improve any of these outcomes, although conclusions may be limited by the smaller sample size in this trial as a result of difficult recruitment.

Whereas the SPPB score did not significantly improve with frequent daily hemodialysis, the increased PHC score is of both statistical and clinical significance. Although the improvement in the PF subscale did not achieve statistical significance, the degree of improvement may also likely be clinically meaningful. Measures of self-reported physical function are well validated metrics and significant predictors of mortality and duration of hospitalization (4,12). Of note, there are important limitations to the assessment of physical performance, particularly in chronic hemodialysis patients. Tests of physical performance do not effectively assess ADLs, a major contributor to overall quality of life in this population, and are prone to ceiling effects, thus they may not detect changes in response to an intervention as effectively as self-reported physical function (13). In fact, it is not uncommon for studies to demonstrate differing results from self-reported versus functionally measured physical performance, because these tests are designed to assess different abilities (e.g., ADLs) (13). Thus, the lack of change in the SPPB score does not detract from the importance of the improvement in self-reported physical function (the PHC score and tendency to improve the PF score).

In the FHN trial, the degree of improvement in both the PHC score and the PF subscale compared with conventional dialysis was greater than in the HEMO study of increased intensity of hemodialysis sessions. Even after adjustment, both metrics were improved by >3.0 points in the FHN trial, which the authors pre-specified as clinically meaningful. This would suggest that the degree of improvement may translate to a reduction in subsequent morbidity and disability. This is consistent with the significant reduction in the primary outcome of mortality in the FHN trial (1). Although the present study cannot determine whether the improvement in self-reported physical function contributed to a reduction in mortality, it has been previously suggested that for every 5-point increase in the PHC score, there is a 10% increase in the probability of survival (14).

The negative findings in the nocturnal FHN trial should be interpreted cautiously because of the smaller sample size compared with the daily trial. Given that solute clearance is even greater with frequent nocturnal versus daily hemodialysis (15), the benefits of frequent daily dialysis may also hold true for nocturnal hemodialysis, but may have been missed due to a lack of power. An additional limitation of this study, as noted by the authors, is that the benefits associated with frequent
Hemodialysis may come at the cost of higher vascular access-related comorbidities. Thus, it is important to carefully weigh the benefits against this potentially increased risk.

The findings from the FHN trial pose several important questions that merit future research. What are the physiologic mechanisms by which frequent dialysis may improve physical function? Furthermore, what are the mechanisms contributing to impaired physical function with ESRD? Although some insight into these questions is presently available, a better understanding of both of these questions will allow for optimization of treatment in this population. For example, coupling frequent dialysis with another intervention(s) (e.g., exercise) targeting these contributing physiologic mechanisms may lead to even greater improvements in physical function. We find it particularly interesting that the improvements in both the PHC score and PF score in the FHN trial were similar in magnitude to changes demonstrated previously with exercise interventions (16–18).

There is also notable overlap in the physiologic mechanisms by which exercise and frequent hemodialysis may improve physical function. We propose a working hypothesis (Figure 1) that via overlapping physiologic mechanisms, the synergistic effect of frequent hemodialysis and exercise may produce additional improvements in physical function.

As shown in Figure 1, common pathways converge on increased physical function as a result of frequent hemodialysis, exercise, or in both modalities. Note, the links between mechanisms are not meant to be exclusive but are simplified for the sake of digestibility. As shown in the diagram, both frequent hemodialysis and exercise may improve physical function via increased delivery of oxygen to skeletal muscle mitochondria, increased clearance of metabolic byproducts, and reduced skeletal muscle catabolism. Enhanced skeletal muscle mitochondrial oxidative capacity may occur following regular exercise via increased capillary density and consequently improved nitric oxide bioavailability and reduced endothelial dysfunction (19). Improved endothelial function may also increase skeletal muscle blood flow, thereby improving clearance of metabolic byproducts, as well as enhancing delivery of substrate (20). Frequent hemodialysis may also increase nitric oxide bioavailability by improving clearance of uremic toxins (21), which affects the downstream pathways discussed above. Both frequent dialysis and exercise are associated with reduced inflammation (22,23), which may improve anemia and thus oxygen delivery to skeletal muscle (24). Inflammation is also tightly linked to oxidative stress, which may induce cellular oxidative damage (24). Frequent hemodialysis also provides better hemodynamic stability as a result of less fluctuation in intravascular fluid volume, which may reduce cellular and vascular damage (25) and improve leg cramping (26), which may otherwise limit the ability to perform physical activity.
Frequent hemodialysis and exercise are also both associated with improved nutritional status (27,28), which may reduce skeletal muscle catabolism, thus improving physical function. In turn, the ability to tolerate future physical activity may be increased, and greater activity itself can continue to improve physical performance. Skeletal muscle catabolism may be further reduced via an improvement in metabolic acidosis (29) as a consequence of enhanced solute removal with frequent hemodialysis (30). In addition to urea, frequent hemodialysis increases removal of phosphorus (15), which may reduce oxidative stress (31), as well as improve skeletal muscle mitochondrial metabolism via lowering of parathyroid hormone (32). Interestingly, intradialytic exercise further enhances both urea and phosphorus removal (33,34).

Given the available evidence that intradialytic exercise can enhance hemodialysis efficiency and improve physical function (35,36), it seems logical to evaluate the efficacy of frequent daily intradialytic exercise for improving physical function in ESRD patients. As both interventions have overlapping physiologic mechanisms, the combination of frequent hemodialysis and exercise may have a synergistic effect and improve physical function to an even greater degree than in the FHN trial. Given the results of the FHN trial, this question merits future research.

Disclosures

None.

References

30. Chan CT, Notarius CF, Merlocco AC, Floras JS: Improvement in exercise duration and capacity after conversion to nocturnal


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See related article, “Effects of Six versus Three Times per Week Hemodialysis on Physical Performance, Health, and Functioning: Frequent Hemodialysis Network (FHN) Randomized Trials,” on pages 782–794.