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The effect of frequent hemodialysis on nutrition and body composition: Frequent Hemodialysis Network Trial

George A. Kaysen[1,2,3], Tom Greene[4], Brett Larive[5], Ravindra L. Mehta[6], Robert M. Lindsay[7], Tom A. Depner[1], Yoshio N. Hall[8], John T. Daugirdas[9] and Glenn M. Chertow[10], and the FHN Trial Group

[1]Department of Medicine, Division of Nephrology, University of California, Davis School of Medicine, Davis, California, USA; [2]Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, Davis, California, USA; [3]Department of Veterans Affairs, Northern California, Mather, California, USA; [4]Department of Biostatistics, University of Utah School of Medicine, Salt Lake City, Utah, USA; [5]Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, Ohio, USA; [6]Division of Nephrology, Department of Medicine, University of California San Diego, San Diego, California, USA; [7]Division of Nephrology, University of Western Ontario and London Health Sciences Center, London, Ontario, Canada; [8]Kidney Research Institute, University of Washington, Seattle, Washington, USA; [9]Division of Nephrology, University of Illinois at Chicago, Chicago, Illinois, USA and [10]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Palo Alto, California, USA

We investigated the effects of frequency of hemodialysis on nutritional status by analyzing the data in the Frequent Hemodialysis Network Trial. We compared changes in albumin, body weight, and composition among 245 patients randomized to six or three times per week in-center hemodialysis (Daily Trial) and 87 patients randomized to six times per week nocturnal or three times per week conventional hemodialysis, performed largely at home (Nocturnal Trial). In the Daily Trial, there were no significant differences between groups in changes in serum albumin or the equilibrated protein catabolic rate by 12 months. There was a significant relative decrease in predialysis body weight of 1.5 ± 0.2 kg in the six times per week group at 1 month, but this significantly rebounded by 1.3 ± 0.5 kg over the remaining 11 months. Extracellular water (ECW) decreased in the six times per week compared with the three per week hemodialysis group. There were no significant between-group differences in phase angle, intracellular water, or body cell mass (BCM). In the Nocturnal Trial, there were no significant between-group differences in any study parameter. Any gain in 'dry' body weight corresponded to increased adiposity rather than muscle mass but was not statistically significant. Thus, frequent in-center hemodialysis reduced ECW but did not increase serum albumin or BCM while frequent nocturnal hemodialysis yielded no net effect on parameters of nutritional status or body composition.

Correspondence: *George A. Kaysen, Department of Medicine, Division of Nephrology, University of California Davis School of Medicine, One Shields Avenue, Genome and Biomedical Sciencies Facility Room 6311, Davis 95616, California, USA. E-mail: gakaysen@ucdavis.edu*

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Chronic kidney disease is often accompanied by reductions in serum albumin and prealbumin, and progressive loss of muscle and adipose tissue, likely due to inadequate macronutrient intake, inflammation,[1] metabolic acidosis,[2,3] reduced physical activity,[4] or a combination of these processes.[5–7] Protein-energy wasting generally tends to progress slowly once dialysis is initiated.[8,9] Although several putative causal factors may be corrected by better control of uremia, the Mortality and Morbidity in Hemodialysis (HEMO) Study showed no associations between increased dialysis dose administered three times weekly and biochemical proxies of protein-energy wasting assessed by caliper anthropometry.[10] Frequent ('daily') hemodialysis has been reported to preserve nutritional status.[11–13] Previous studies of frequent hemodialysis were not randomized, typically had small sample sizes, and used anthropometric measures of body composition.

The Frequent Hemodialysis Network (FHN) Trials aimed to examine the effects of increased hemodialysis frequency on multiple intermediate outcome measures, including nutritional status and body composition. Frequent (six times per week) hemodialysis provided as in-center daily or nocturnal at-home hemodialysis was compared with conventional three times weekly hemodialysis. The objectives and protocol summaries of both trials have been previously published.[14] Limited by sample size, the FHN Trials were not designed to assess mortality or major health events.

We have previously reported that in-center and nocturnal frequent hemodialysis interventions failed to increase the 12-month serum albumin concentration, which we stipulated as the primary outcome for the nutritional status domain. In this manuscript, we present treatment effects on equilibrated protein catabolic rate (ePCR), a proxy for dietary protein intake, and body composition, as reflected by bioimpedance-measured resistance, reactance, phase angle, and vector length, as well as derived estimates of intracellular (ICW) and extracellular water (ECW) and body cell mass (BCM).

RESULTS

A total of 245 subjects were randomized in the Daily Trial, and 87 subjects were randomized in the Nocturnal Trial. Baseline characteristics are summarized in Table 1. Subjects participating in both trials were diverse in terms of age, sex, race/ethnicity, and other clinical characteristics. Although the two trials were not formally compared, end-stage renal disease vintage was shorter and residual kidney function higher in the Nocturnal Trial. Although we had planned to evaluate the effects of frequent hemodialysis on multiple aspects of nutritional status and body composition, our primary outcome within the nutrition domain was the change in serum albumin concentration from baseline to end of treatment (12 months). There were significant treatment differences in weekly standard Kt/V_{urea}, and per-session and weekly ultrafiltration volume, as previously reported.[15,16]

Serum albumin concentration

In the Daily Trial, predialysis serum albumin increased 1 month after randomization in the frequent compared with conventional ($3\times$/week) group (relative difference 0.06 g/dl, 95% confidence interval (-0.01 to $+0.13$ g/dl)). This difference was statistically significant over months 3–5 but was not sustained at 12 months. The change in albumin from baseline to 12 months did not differ significantly between treatment arms in either trial (Table 2, Figure 1a and b). On the basis of a regression of serum albumin on the preceding interdialytic interval, we estimated that the shorter average interdialytic interval in the six times vs. the three times per week group contributed 0.057 ± 0.013 g/dl to the treatment difference in serum albumin concentrations. Once this sampling bias was accounted for, the changes in serum albumin did not differ significantly between the treatment groups at any follow-up time. In the Nocturnal Trial, there were no significant between-group differences at any time, although in both groups combined serum albumin increased by 0.19 ± 0.04 g/dl ($P<0.001$; Table 2, Figure 1b).

Equilibrated protein catabolic rate

For both the Daily and Nocturnal Trials, there were no significant differences in ePCR between the treatment groups at 1, 4, or 12 months (Figure 1c and d). In the Nocturnal Trial, mean ePCR increased by 9.1 ± 2.6 g/day from baseline to 12 months in both treatment groups combined (Figure 1d). The increases in serum albumin and ePCR persisted and remained statistically significant compared with baseline when the Nocturnal Trial analysis was restricted to patients with baseline glomerular filtration rate <1.70 ml/min, the median baseline glomerular filtration rate.

Body weight

In the Daily Trial, there was a significant relative decrease (frequent vs. conventional) in predialysis body weight evident within 1 month (Figure 2a). Between 1 and 12 months, the relative change in predialysis body weight was 1.3 ± 0.5 kg ($P=0.007$) higher in the 6 times per week group. Postdialysis body weight changed in parallel in both treatment groups (Figure 2b). Between 1 and 12 months, the relative change in postdialysis body weight was 1.1 ± 0.5 kg ($P=0.04$) higher in the 6 times per week group.

In the Nocturnal Trial (Table 2, Figures 2c and d), pre- and postdialysis weights in both treatment groups combined decreased by 1 month after baseline, reaching a nadir at 2 months, with a slow increase toward and then beyond baseline by 12 months, but with no significant difference between treatment groups.

Measured parameters: reactance, resistance, phase angle, and vector length

In the Daily Trial, there were statistically significant relative increases in measured reactance and resistance in the 6 times per week group at months 4 and 12. The vector length was relatively lengthened in the 6 times per week group, reflecting reduced tissue hydration (Table 2).

In the Nocturnal Trial, none of the between-group comparisons reached statistical significance, with the exception of vector length at 4 months, where the vector length was significantly lengthened in the 6 times per week group (Table 2).

Derived estimates of body composition

In the Daily Trial, there were large relative decreases (frequent vs. conventional) in total body water (TBW) evident at 1 month, which remained statistically significant at 4 and 12 months (Table 2, Figure 3a). The relative reduction in TBW was confirmed using an independent determination of the urea distribution volume from monthly urea kinetic modeling (Table 2, Figure 3b). Changes in estimates of ECW mirrored those of TBW (Figure 3c), suggesting that the relative decline in TBW was driven by a change in ECW, an observation consistent with the changes in vector length described above. There were no significant relative changes in ICW (Table 2, Figure 3d). Relative changes in TBW, ECW, and ICW during the Nocturnal Trial were small in magnitude and not statistically significant (Table 2, Figure 4).

There was a relative increase in estimated adiposity in the 6 times per week group, although these changes did not reach statistical significance in either trial (Table 2, Figures 5a and c). Similarly, there were no statistically significant relative changes in ICW or BCM, the metabolically active component of lean body mass (Table 2, Figures 5b and d). Indeed, the relative *decrease* in lean body mass could be explained