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Short daily hemodialysis is associated with lower plasma FGF23 levels when compared with conventional hemodialysis

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ABSTRACT

Background. The utilization of short-term daily hemodialysis has increased over the last few years, but little is known on its effects on the control of serum phosphate and fibroblast growth factor 23 (FGF23) levels.

Methods. We therefore performed a cross-sectional study to compare FGF23 levels as well as other biochemical variables between 24 patients undergoing short daily hemodialysis using the NxStage System[®] and 54 patients treated with conventional in-center hemodialysis. FGF23 levels were measured using the second-generation Immotopics[®] C-terminal assay.

Results. Short daily hemodialysis patients were younger than patients on conventional hemodialysis but there were no differences between groups in the duration of end-stage renal disease nor in the number of patients with residual renal function. A greater number of short daily hemodialysis patients received vitamin D sterol therapy than did conventional in-

center hemodialysis patients while there were no differences in the use of different phosphate binders and calcimimetic therapy between groups. Overall serum calcium, phosphorus and intact parathyroid hormone levels were similar between groups. While serum phosphorus levels correlated with FGF23 concentrations in each group separately [$r = 0.522$ ($P < 0.01$) and $r = 0.42$ ($P < 0.01$) in short daily and conventional in-center hemodialysis, respectively], FGF23 levels were lower [823 RU/mL (263, 2169)] in the patients receiving short daily hemodialysis than in patients treated with conventional hemodialysis [2521 RU/mL (909, 5556)] ($P < 0.01$ between groups).

Conclusions. These findings demonstrate that FGF23 levels are significantly lower in short daily hemodialysis patients and suggest that FGF23 levels may be a more sensitive biomarker of cumulative phosphate burden than single or multiple serum phosphorus determinations in patients treated with hemodialysis.

Keywords: dialysis adequacy, FGF23, hemodialysis

INTRODUCTION

Over the past decade, nocturnal dialysis or longer session lengths have been explored as an alternative to in-center thrice weekly hemodialysis. A variety of studies have demonstrated that these alternative regimens improve control of serum phosphorus, reduce phosphate binder requirements and allow for a liberalization of diet [1–3]. The increased phosphate removal may at times be so marked as to necessitate the addition of phosphate to the dialysate bath [3–5].

Concurrently, over the last decade, fibroblast growth factor 23 (FGF23) has gained recognition as a key regulator of phosphate and vitamin D metabolism. FGF23 levels are extremely elevated in dialysis patients [6], values correlate with serum phosphorus concentrations [7, 8] and increase with both enteral phosphate intake [9] and with vitamin D sterol therapy [10]. Interestingly, although serum phosphorus concentrations themselves have long been associated with cardiovascular disease and mortality in patients treated with maintenance dialysis, FGF23 has also been identified as an independent predictor of heart disease and mortality in both the general and dialysis population [6, 11–13].

Recently, short daily hemodialysis, in which dialysis is performed 6–7 days a week, has also gained increasing popularity [14]. This dialytic modality is targeted to achieve a similar dialysis adequacy, assessed by a standardized weekly K_t/V (std K_t/V) as conventional in-center hemodialysis. However, short daily hemodialysis results in a higher weekly phosphate clearance [15]. Due to its large volume of distribution, increased phosphate removal may not necessarily result in lower serum phosphorus levels. In contrast, it has been postulated that FGF23, which is produced by bone and whose expression correlates with bone mineralization [16], may more accurately reflect total body phosphate burden [17]. Thus, the goal of the current study was to compare FGF23 levels between patients undergoing short daily hemodialysis using the NxStage System[®] and patients treated with conventional in-center hemodialysis.

PATIENTS AND METHODS

All patients aged 18–80 years, undergoing conventional maintenance dialysis and short daily hemodialysis at Davita Century City, Davita South Valley, and Davita Simi Valley for at least 3 months from 01/01/2009 through 7/1/2012, were considered as potential candidates for the study and were selected for inclusion if they agreed to give informed consent. In-center dialysis was performed utilizing the Fresenius 2008K three times weekly with the dialysis prescription targeting a goal K_t/V of >1.4 . Short daily dialysis was performed at the patients home utilizing the NxStage System One performed 5 or 6 days a week with a targeted standardized K_t/V (std K_t/V) of 2. Phosphate binders along with active vitamin D, calcimimetics and erythropoietin therapy were prescribed at the discretion of the treating physicians. The study was approved by the UCLA Human

Subject Protection Committee and informed consent was obtained from all patients and/or parents.

Demographic data, including patient age, gender, weight, ethnicity, cause of renal insufficiency, and dialysis vintage, phosphate binders, vitamin D therapy, calcimimetics, residual renal function as well as weekly clearance (std K_t/V) and biochemical data, including hematocrit, creatinine and circulating levels of calcium, phosphorus, PTH and FGF23, were obtained. Biochemical values were obtained immediately prior to the dialysis treatment (48 h after the prior treatment in the conventional group and 24 h after the prior treatment in the short daily hemodialysis group). Three serial serum phosphorus concentrations were collected over 3 months prior to the cross-sectional analysis to obtain a time-average assessment of circulating phosphorus concentrations. Anuria was defined as a urine output of <50 mL/day. Standardized K_t/V was calculated via the Leypoldt equation [18]. Biochemical determinations for serum calcium and phosphorus were determined using an Olympus AU5400 (Olympus America Incorporated, Center Valley, PA). PTH levels were measured in plasma by a second-generation assay (Immutopics, San Clemente, CA; normal range: 10–65 pg/mL) and FGF23 levels were determined in plasma using the second-generation C-terminal assay (Immutopics, San Clemente, CA).

Results are reported as mean \pm standard deviation for variables with normal distributions; the median (interquartile range) is presented for all other parameters. Dichotomous variables are reported as percentage (95% confidence interval). Spearman correlation coefficients were used to describe the correlation between two variables; linear regression was used to assess the relationship between biochemical (PTH, calcium, phosphorus) and demographic (age, dialysis vintage) variables and circulating FGF23 values. Variables with non-normal distributions were transformed prior to regression analysis.

RESULTS

Patient demographics

Fifty-four patients treated with conventional (thrice weekly) hemodialysis and 24 patients receiving short daily hemodialysis aged 60.8 ± 2.6 and 45.3 ± 4.7 years, respectively ($P < 0.05$), and weighing 68 ± 16.3 and 74 ± 16.8 kg, respectively ($P = \text{NS}$) were included in this study. The duration of end-stage renal disease was 2.8 years (1.2, 4.3) and 2.8 years (1.1, 7.6) in the two groups, respectively ($P = \text{NS}$) with a dialysis treatment duration of 2.4 (1.2, 4.1) and 2.8 (1.1, 7.6) in the two groups, respectively ($P = \text{NS}$). Fourteen patients treated with conventional hemodialysis (26%) and six of those treated with short daily hemodialysis (24%) had previously received kidney transplantation (NS between groups). Forty-nine of the conventional hemodialysis patients were anuric while 21 of the short daily hemodialysis patients were anuric (NS between groups). More patients treated with short daily hemodialysis (54%) received vitamin D sterols than did patients receiving conventional hemodialysis (11%) ($P < 0.01$ between groups). Neither the use of calcimimetic nor type of phosphate binder differed between the two dialytic modalities as shown in Table 1.

Table 1. Biochemical values in patients treated with conventional hemodialysis and in those treated with short daily hemodialysis

	Conventional (n = 54)	Short daily (n = 24)
Age	60.8 ± 18.9	47.3 ± 18.3*
Weight (kg)	68 ± 16.3	74 ± 16.8
Dialysis vintage (years)	2.8 (1.3, 4.2)	2.8 (1.1, 7.6)
Hgb (mg/dL)	12.0 ± 1.5	11.4 ± 1.4
Std K_t/V	2.35 (2.18, 2.52)	2.40 (2.23, 2.73)
Albumin (g/dL)	4 (3.6, 4.2)	4.2 (4, 4.4) [†]
Calcium (mg/dL)	8.7 ± 0.7	8.8 ± 0.6
Phosphorus (mg/dL)	5.0 ± 1.3	4.9 ± 1.2
Time-averaged phosphorus (average of 3 months prior to the study) (mg/dL)	5.0 ± 1.3	5.0 ± 1.2
iPTH (pg/mL)	237 (131, 321)	198 (106, 395)
FGF23 (RU/mL)	2521 (909, 5556)	823 (263, 2169)*
Vitamin D use [% (95% CI)]	11 (4–23)	54 (33–74)*
Calcimimetic use [% (95% CI)]	44 (31–59)	46 (26–67)
Phosphate binder use [% (95% CI)]	81 (69–91)	79 (58–93)
Calcium-containing binder use [% (95% CI)]	33 (21–47)	25 (10–47)
Phosphate binding equivalents (mg/day)	207 ± 182	191 ± 156

* $P < 0.01$ between groups.

[†] $P < 0.02$ between groups.

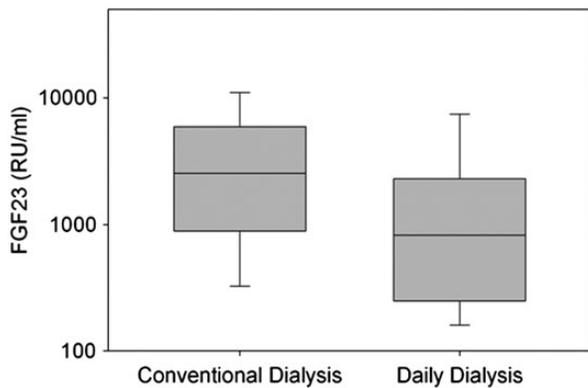


FIGURE 1: Serum FGF23 in conventional hemodialysis and in those treated with short daily hemodialysis. Serum FGF-23 was significantly higher in those treated with conventional hemodialysis (median 2521 RU/mL) versus those treated with short daily hemodialysis (median 823 RU/mL). Box plots demonstrate 25th, 50th and 75th percentiles with error bars spanning 10–90th percentiles.

* $P < 0.01$.

Biochemical values

Biochemical values are displayed in Table 1. Hematocrit, calcium, phosphorus and time-averaged serum phosphorus, and PTH concentrations did not differ between groups as well as K_t/V . Serum albumin was slightly lower in the conventional hemodialysis group ($P < 0.02$). Interestingly, plasma FGF23 values were lower in those patients treated with short daily hemodialysis when compared with conventional hemodialysis ($P < 0.01$), despite equivalent levels of serum phosphorus and PTH and the greater use of vitamin D sterols in patients

receiving daily hemodialysis (Figure 1). This result was unchanged when the analysis only included anuric patients. Additionally there was no association between duration of dialysis and FGF23 levels in either group. As anticipated, phosphorus levels correlated with FGF23 concentrations in both groups, ($r = 0.42$, $P < 0.01$) and $r = 0.52$, $P < 0.01$), respectively, in patients treated with conventional hemodialysis and in those receiving short daily hemodialysis, (Figure 2). When adjusting for modality, age, calcium, phosphate binding equivalency, vitamin D therapy (yes/no), and calcimimetic therapy (yes/no), serum phosphate and plasma PTH levels were independent predictors of circulating plasma FGF23 concentrations.

DISCUSSION

The current study confirms that, in patients treated with maintenance dialysis, circulating FGF23 values are elevated and they correlate with serum phosphorus concentrations. Interestingly, however, values of FGF23 were lower in patients receiving short daily hemodialysis when compared with conventional hemodialysis, despite greater use of vitamin D sterols and equivalent serum phosphorus and PTH concentrations.

The discrepancy between circulating FGF23 values and circulating phosphate concentrations highlights important limitations with the use of serum phosphorus levels in the assessment of phosphate burden in the CKD population. Currently, the assessment of bone disease is recommended using target circulating mineral ion concentrations and parathyroid hormone levels; however, a growing body of evidence suggests that circulating FGF23 is another important modifier of the indices of bone and mineral metabolism in CKD, both as potential predictor of off target tissue effects and as a reflection of phosphate balance and therapy with active vitamin D sterols and/or calcimimetics [9, 10, 19, 20]. Indeed, increased values of FGF23 have been associated with cardiovascular disease and increased mortality rates across the spectrum of CKD as well as in the general population [6, 13]. Moreover, experimental data have demonstrated that FGF23 directly induced left ventricular hypertrophy in rodents through non-traditional FGF23 metabolic pathways [21].

While numerous studies have linked serum phosphorus concentrations [10, 20, 22] to increased circulating FGF23 levels, the current study suggests that FGF23 may be an even more sensitive biomarker for total body phosphate stores than circulating phosphorus concentrations by itself. Indeed, 80–90% of total body phosphate resides in bone [23] and bone is the major buffer for acute changes in the phosphate load, as occurs with meal, or during hemodialysis. Circulating phosphorus concentrations decline rapidly with the initiation of hemodialysis, reaching a steady state at ~120 min [24] and are best estimated via a four-compartment model [25]. Thus, frequent, short daily hemodialysis can remove more phosphate over the long term than does thrice weekly, despite similar urea clearances. Indeed, a recent study demonstrated that patients using the NxStage System One had an average phosphate removal of 694 ± 343 mg per treatment, which corresponded to a weekly removal of 4.16 g

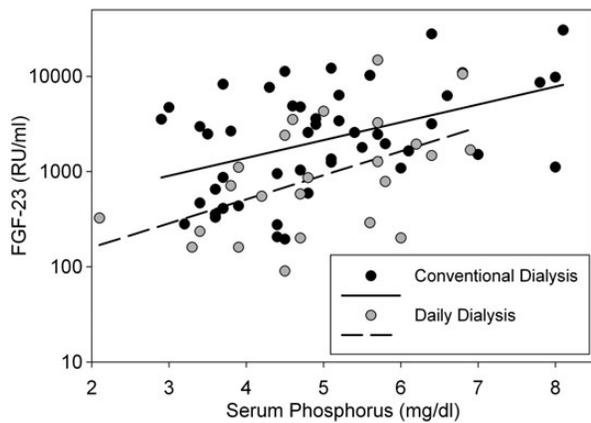


FIGURE 2: Serum FGF23 versus serum phosphorus in conventional hemodialysis and in those treated with short daily hemodialysis. Plasma FGF23 correlated with serum phosphorus in both conventional hemodialysis (black symbols) and in those treated with short daily hemodialysis (grey symbols) with correlations coefficients of $r = 0.42$ ($P < 0.01$) and $r = 0.52$ ($P < 0.01$), respectively.

[15] and contrasted to the weekly removal of 2–3 g of phosphate via thrice weekly high flux hemodialysis [26, 27]. While serum phosphate concentrations are buffered, i.e. maintained, as much as possible, within the normal range—by release and re-uptake of phosphate by bone, chronically increased phosphate burden may only be reflected in the circulation by increased FGF23 levels. Thus, the current study suggests that FGF23 levels may be a more sensitive biomarker of cumulative phosphate burden than a single or even multiple serum phosphorus determinations.

The present study also demonstrates a potential shortcoming in the current methods for assessing dialysis adequacy which are based solely on changes in circulating urea concentrations and not on other important parameters such as phosphate removal. Indeed, a recent study demonstrated that only 28% of the variation in phosphate removal during thrice weekly hemodialysis is explained by K_t/V_{urea} [28]. In the current study, short daily hemodialysis dosages as measured by standardized K_t/V were similar to conventional hemodialysis dosages yet significant differences in circulating FGF23 values were observed, potentially reflecting that short-term frequent dialysis sessions are able to achieve a higher removal of phosphate per week than do the less-frequent, longer dialysis sessions associated with conventional HD.

The cross-sectional nature of this study prevents the exclusion that bias by indication may have affected the reported findings. The two study groups were similar in terms of standardized K_t/V and dialysis vintage. Importantly, given the effects of residual renal function on serum FGF23 levels in peritoneal dialysis patients [8, 29] and conventional hemodialysis [30], both groups in the current study contained the same distribution of patients with residual renal function. Different types of phosphate binders have been shown to have dissimilar effects in reducing FGF23 [31, 32]; however, the distribution of binders was similar between both groups. The two groups differed in terms of age; patients treated with short daily hemodialysis were younger than those on conventional hemodialysis. In addition,

the short daily hemodialysis group had a marginally higher serum albumin. These discrepancies suggest that other factors, such as dietary phosphate, nutritional status or race may potentially have influenced FGF23 values. In conclusion, the current study demonstrates that FGF23 levels may be a more sensitive biomarker of cumulative phosphate burden than single or multiple phosphorus determinations. Furthermore, dialysis adequacy, as assessed by urea clearance, is imperfect in assessing the clearance of phosphorus, and further prospective trials are warranted to examine the effect of different dialytic regimens on FGF23 levels as well as on morbidity and mortality in patients with end-stage renal disease.

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CONFLICT OF INTEREST STATEMENT

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