Changes in serum inflammatory markers are associated with changes in apolipoprotein A1 but not B after the initiation of dialysis

George A. Kaysen¹,², Lorien S. Dalrymple¹, Barbara Grimes³, Glenn M. Chertow⁴,⁵, John Kornak³ and Kirsten L. Johansen³,⁴,⁶,⁷

¹Department of Medicine, University of California Davis, CA, USA, ²Department of Biochemistry and Molecular Medicine, University of California Davis, CA, USA, ³Department of Epidemiology and Biostatistics, University of California San Francisco, CA, USA, ⁴United States Renal Data System Nutrition Special Studies Center, San Francisco, CA, USA, ⁵Department of Medicine, Stanford University School of Medicine, Palo Alto, CA, USA, ⁶San Francisco Department of Veterans Affairs Medical Center, San Francisco, CA, USA and ⁷Department of Medicine, University of California San Francisco, San Francisco, CA, USA

Correspondence and offprint requests to: George A. Kaysen; E-mail: gakaysen@ucdavis.edu

ABSTRACT

Background. Few studies have examined the changes in lipoproteins over time and how inflammation is associated with lipoprotein concentrations among patients with end-stage renal disease on dialysis. One possible explanation for the association of low LDL cholesterol concentration and adverse outcomes is that inflammation reduces selected apolipoprotein concentrations.

Methods. Serum samples were collected from a subsample of patients enrolled into the Comprehensive Dialysis Study every 3 months for up to 1 year. We examined the relation between temporal patterns in levels of inflammatory markers and changes in apolipoproteins (apo) A1 and B and the apo B/A1 ratio using linear mixed effects modeling and adjusting for potential confounders.

Results. We enrolled 266 participants from 56 dialysis facilities. The mean age was 62 years, 45% were women and 26% were black. Apo A1 was lower among patients with higher Quetelet’s (body mass) index (BMI), diabetes mellitus and atherosclerosis. Apo B was lower among older patients, patients with lower BMI and patients with lower serum creatinine and patients with lower BMI. Over the course of a year, apo A1 changed inversely with serum concentrations of the acute phase proteins C-reactive protein (CRP) and α₁ acid glycoprotein (α₁AG), while apo B did not. Changes in α₁AG were more strongly associated with changes in apolipoprotein concentrations than were changes in CRP; increases in α₁AG were associated with decreases in apo A1 and increases in the apo B/A1 ratio.

Conclusions. Changes in inflammatory markers were associated with changes in apo A1, but not apo B over 1 year, suggesting that reductions in high-density lipoprotein cholesterol are associated with inflammation, either of which could mediate cardiovascular risk, but not supporting a hypothesis linking increased risk of low levels of apo B containing lipoproteins to the risk associated with inflammation.

Keywords: apolipoprotein A1, apolipoprotein B, α₁ acid glycoprotein, CRP, HDL

INTRODUCTION

Chronic kidney disease (CKD) is associated with high cardiovascular risk [1] and exhibits a characteristic pattern of
cardiovascular risk markers, including heightened inflammation and alterations in lipid and lipoprotein levels and structure, typically described as dyslipidemia rather than hyperlipidemia [2] with higher triglyceride levels and lower high-density lipoprotein (HDL) cholesterol levels associated continuously with estimated glomerular filtration rate (eGFR) [3, 4]. Triglycerides are elevated, whereas HDL and low-density lipoprotein (LDL) cholesterol concentrations are usually low [5]. Although lipids themselves manifest expected associations with measures of vascular structure and function, specifically aortic pulse wave velocity [6] and carotid intimal media thickness [7], the relationships among lipoprotein concentrations and mortality in patients on dialysis differ from the relationship observed in the general population, inasmuch as patients on dialysis or with advanced chronic kidney disease with the lowest cholesterol and triglyceride concentrations are those at highest risk [8, 9]. There is evidence that inflammation may modify the associations of lipoproteins with cardiovascular end points in end-stage renal disease (ESRD). Patients with little or no indication of inflammatory activity exhibit the expected relations among lipoproteins and cardiovascular events (i.e., higher levels = higher risk). In contrast, patients with heightened inflammatory activity show paradoxical relations (lower levels = higher risk) [10–14]. Other studies show no persistent inverse association [15–17] in this patient population. An understanding of whether inflammation affects the levels of lipoproteins or modifies lipoprotein-associated risk in another way is essential in order to make sense of these conflicting results, but there have been few cross-sectional [18] and no longitudinal studies relating inflammation to lipidoprotein concentrations to our knowledge.

The Comprehensive Dialysis Study (CDS) was a prospective cohort study in which serum samples were collected every 3 months for 1 year from a group of patients initiating dialysis in facilities within the USA. We sought to examine the temporal patterns in levels of apolipoproteins (apo) A1 and B and the apo B/A1 ratio and to characterize the associations among these apolipoproteins and concurrent measures of acute phase proteins, C-reactive protein (CRP) and α1 acid glycoprotein (α1AG).

### M A T E R I A L S  A N D  M E T H O D S

#### Design and participants

The CDS is a prospective cohort study of adults with ESRD who initiated hemodialysis or peritoneal dialysis between June 2005 and June 2007 in dialysis facilities throughout the USA designed to examine the nutritional status, physical activity and health-related quality of life among incident dialysis patients [19, 20]. The CDS has been previously described in detail, including sampling of dialysis facilities, recruitment and measures [19, 20]. In brief, participants were successfully recruited from 297 dialysis facilities out of 335 selected facilities. Fifty-six of 73 facilities subsampled to participate in the nutrition substudy agreed to participate and provide serum samples. Participants (n = 266) from the 56 facilities provided up to five serum samples each, one at enrollment and quarterly thereafter for up to a year. Facilities were selected a priori by systematic probability sampling proportional to estimated size sampling to participate in the nutrition substudy. The biomarkers chosen for study, albumin, prealbumin, apo B, apo A1, CRP and α1AG were predetermined to establish the longitudinal trajectory of these patients once dialysis was initiated and the relationship between inflammation and both lipoproteins and nutritional biomarkers, as previously reported [20]. Sex, age and the comorbidities used for analysis were selected and predetermined during the design of this study.

The study was approved by the Institutional Review Boards of the University of California, San Francisco Emory University and the University of California Davis and all patients provided informed consent for participation.

#### Data collection

Data on demographics, body composition (height and weight), dialysis modality and access, comorbidities and serum creatinine at dialysis initiation were collected from the CMS Medical Evidence Form (CMS 2728) and a telephone interview administered by DataBanque Research Services (Pittsburgh, PA). Blood samples were collected at enrollment and quarterly for up to 1 year.

#### Exposure and outcome

The primary exposures of interest were longitudinal measures of acute phase proteins, CRP and α1AG. The primary outcomes of interest were longitudinal measures of apolipoprotein A1, B and the ratio of apolipoproteins (apo B/ apo A1). Apo A1, CRP and α1AG concentrations were measured in duplicate on each serum sample using a Beckman Array 360 nephelometer (Beckman, La Brea, CA), and apo B was measured in duplicate on each serum sample with a PolyChem chemical analyzer (Polymedco Cortlandt Manor, NY). We used the mean concentration of the duplicate serum concentrations of each analyte in analyses. Intra-assay coefficients of variation (CoV) were as follows: apo A1 1.1%, apo B 1.1%, CRP 3.6% and α1 AG 0.14%. Inter-assay CoV were as follows: apo A1 3.2%, apo B 5.4%, CRP 9.2% and α1AG 3.1–5.5%.

#### Statistical analyses

We considered how changes in acute phase proteins were associated with changes in each apolipoprotein during 1 year of dialysis. Statistical modeling was based on linear mixed effects models with random intercept terms for dialysis center to account for within-center correlations (clustering by dialysis center). We adjusted for confounding by including baseline patient characteristics as covariates. We preselected demographic (age, sex, race) and clinical covariates (diabetes mellitus, atherosclerotic vascular disease, modality and vascular access) and nutritional status (BMI and serum creatinine concentration), which might confound the relations among inflammatory markers and lipoprotein concentrations in the initial design of this study. We additionally incorporated sampling weights based on the CDS survey design in order to generate population representative estimates from the original stratified sampling (using robust standard error estimates).
Lowess curves of each apolipoprotein versus each of the two time-varying independent variables, CRP and α1AG, were examined to determine whether the assumption of linearity was appropriate. CRP was log-transformed for analyses. The linear mixed effects models included time specified as equally spaced units representing each quarterly blood draw, time varying longitudinal measures of CRP and α1AG (measured at enrollment and quarterly for up to 1 year) and potential confounders measured only at baseline (age, sex, race, body mass index (BMI), dialysis modality and access, serum creatinine and comorbidities).

Baseline measured covariates were included as fixed effects with an interaction with time. Longitudinal measures were included as (fixed-effect) time-varying covariates. Our model building strategy was to include all covariates in an initial model without any interactions and add in the baseline covariate interactions with time individually. All the baseline by time interactions with P < 0.05 from the individual models were then included together in a single model, from which we dropped terms one at a time (based on dropping the term with the highest P-value) and refitting the model until all remaining interaction terms had P-values < 0.05. We further examined the inclusion of quadratic terms for continuous baseline predictors and their interactions with time in the model to account for any potential non-linearity, and retained the quadratic terms when appropriate. Diagnostic tests of the final fitted models (QQ plots, Cook’s D statistics) were performed to check that modeling assumptions were met and that results were not unduly influenced by outlying centers.

All measurements were included from all patients in the final analyses. Two sensitivity analyses were performed to address the issue of bias arising from patient dropout. First, models were run including measurements from only those participants who provided a serum sample at 12 months (end of study). As a further check, final models were run including all the data and two additional predictors, a predictor equal to the number of the last blood draw for each individual and a predictor equal to the interaction of last draw with time. Results from both analyses were similar to that resulted from the primary analyses. All statistical analyses were performed using SAS 9.2 (Cary, NC).

### RESULTS

We included 266 CDS nutrition substud y participants from a total of 56 dialysis facilities (Table 1). The mean age was 62 years, 45% were women and 26% were black.

**Association of baseline patient characteristics with apolipoproteins during follow-up**

Associations of apo A1 with patient characteristics seen in the final multiple predictor model were similar to those observed in the general population, with statistically significantly higher levels among women and lower levels among patients with higher BMI, diabetes mellitus and atherosclerosis (Table 2). Furthermore, age was a statistically significant correlate of apo A1 concentrations.

<table>
<thead>
<tr>
<th>Baseline characteristic, n = 266</th>
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<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>62 (14)</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>147 (55)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>189 (71)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>68 (26)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>29.8 (7.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL</strong></td>
<td>6.20 [4.70, 8.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>152 (57)</td>
<td></td>
</tr>
<tr>
<td><strong>Atherosclerosis</strong></td>
<td>96 (36)</td>
<td></td>
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<tr>
<td><strong>Heart failure</strong></td>
<td>85 (32)</td>
<td></td>
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<tr>
<td><strong>Dialysis modality and access</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis, AVF or AVG</td>
<td>63 (24)</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis, catheter</td>
<td>181 (68)</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>22 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline concentration of time-varying analyte</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline apo A1, mg/dL</td>
<td>141 (34.7)</td>
<td></td>
</tr>
<tr>
<td>Baseline apo B, mg/dL</td>
<td>84 (27.2)</td>
<td></td>
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<tr>
<td>Baseline ratio apo B/apo A1</td>
<td>0.58 [0.18, 1.74]</td>
<td></td>
</tr>
<tr>
<td>Baseline α1AG, mg/dL</td>
<td>115 (35.9)</td>
<td></td>
</tr>
<tr>
<td>Baseline C reactive protein, mg/L</td>
<td>7.45 [3.95, 12.75]</td>
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</table>

Data presented as mean (SD), number (%) or median [interquartile range]; AVF or AVG: arteriovenous fistula or arteriovenous graft.

* One male with missing BMI was assigned average BMI value for males.
* From USRDS 2728 form.
* One hemodialysis patient with missing access type was assigned catheter.

Patients with lower BMI, older individuals and patients with higher serum creatinine concentration had lower levels of apo B. Patients on peritoneal dialysis had significantly higher apo B concentrations when compared with patients on hemodialysis with an arteriovenous fistula or graft. The ratio of apo B/apo A1 was significantly lower in older patients, marginally lower in women and higher among patients with higher BMI.

**Changes in lipoproteins over time**

During 1 year of observation, the mean apo A1 concentrations decreased from the baseline during the first two quarters and returned to baseline values by the last quarter. Apo B showed no consistent change over time. Since apo B, unlike apo A1, did not vary substantially over time, the temporal relationship of the ratio was mostly related to changes in apo A1 and exhibited a similar (but inverted) curvilinear pattern. Serum creatinine was statistically significantly associated with the pattern of change of apo A1 and the ratio. Specifically, there were statistically significant interactions between creatinine and time, leading to a pattern where the U-shape was ‘wider’ among patients with higher serum creatinine concentrations. However, the inclusion or exclusion of these creatinine interactions with time did not substantially change the other primary associations of interest in the models (data not shown). We retained these terms in our models because of our prespecified modeling strategy.

**Association of lipoprotein changes with inflammation**

Figures 1–3 demonstrate the unadjusted relationships between changes in the levels of α1AG and changes in apolipoprotein concentrations. Increases in α1AG were associated
with decreases in apo A1 (Figure 1) \((r^2 = 0.11, P < 0.0001)\) and increases in the ratio of apo B/apo A1 (Figure 2) \((r^2 = 0.03 P < 0.0001)\). Changes in CRP exhibited similar associations (data not shown). In contrast to apo A1, changes in neither α1AG (Figure 3) \((r^2 = 0.003 P = 0.13)\) nor in CRP (data not shown) were associated with changes in apo B concentration.

Adjusted analyses are presented in Table 2 and Supplementary data, Tables S1 and S2. Changes in α1AG were associated inversely with changes in apo A1 and directly with that in the ratio of apo B/apo A1, and were not independently associated with changes in apo B (Table 2). Changes in CRP were significantly inversely associated with changes in apo A1, but not with apo B or the ratio of apo B/apo A1 (Supplementary data, Table S1). When changes in both inflammatory markers were considered simultaneously, the estimated associations with both inflammatory markers were attenuated (Supplementary data, Table S2). The associations of changes in α1AG with changes in apo A1 and changes in the ratio of apo B/apo A1 remained statistically significant. Although changes in CRP were also inversely related to changes in apo A1, the association was no longer significant once α1AG was accounted for in the model (Supplementary data, Table S2). Consequently, based on our model building process, our final models included only α1AG as a measure of inflammation (Table 2).

**DISCUSSION**

In this cohort of patients new to dialysis, we found that associations of lipoproteins with patient characteristics mostly paralleled those observed in the general population. Longitudinal data showed that apo A1 concentrations exhibited a curvilinear trajectory, first decreasing, then increasing and returning to approximately baseline levels after 1 year. In contrast, apo B levels did not show a consistent pattern of change over a 1-year period, and consequently the apo B/apo A1 ratio varied mostly according to changes in the apo A1 concentration. Changes in apo A1, but not apo B showed a significant pattern of association with markers of inflammation.

Apo A1 is the principal apolipoprotein contained in HDL [21], and apo B occurs as a single molecule in LDL, very-low-density lipoprotein (VLDL) and chylomicron and VLDL remnant particles making up intermediate density lipoproteins. Apo A1, apo B and the ratio of apo B/A1 are associated with cardiovascular risk in non-ESRD and ESRD populations [22], HDL levels decrease with increasing adiposity in individuals without CKD [23], and low HDL cholesterol and low apo A1 are risk factors for loss of kidney function [24, 25] as is a higher apoB/A1 ratio [26]. Our study indicated that Apo A1, but not apo B, was associated with the comorbidity of atherosclerosis, in contrast to what was reported in the ARIC study [27]. The relation between high BMI and low HDL is progressively attenuated as eGFR declines [4], and so it is interesting that we observed an inverse association between BMI and apo A1 even in this cohort of patients on dialysis. HDL cholesterol has not been previously observed to be associated with age in cross-sectional studies [28–31], and HDL levels have been observed to decrease with time in prospective observational studies [32–34] among individuals without kidney disease. In contrast, we found that apo A1 was higher among older patients in our cohort.

The relation between inflammation and apolipoprotein levels may be complex and bi-directional. Inflammation and the acute phase response cause increases in triglyceride levels as a consequence of increased synthesis of VLDL [35], while both LDL and HDL cholesterol concentrations are decreased
in the setting of inflammation in the general population [36, 37]; these changes may play a role in altering vascular structure [36, 38]. While apo A1 has been described as an agent that directly suppresses cytokine production [39, 40] and thus potentially plays an anti-inflammatory role, infectious events have been documented to both alter endothelial function and suppress apo A1 levels and increase apo B/A1 ratios in patients without kidney disease [41]. TNF-α has been shown to directly downregulate Apo A1 gene expression [42, 43] and HDL levels have been reported to be decreased following infectious events in previously healthy children [44]. In addition, inflammation could act indirectly to lower HDL and LDL by causing anorexia. On the other hand, atherosclerotic plaques resulting from increased levels of triglyceride-rich and apo B-rich lipoproteins are thought to be one source of inflammation [45–47], linking lipoprotein levels to inflammation through a causal path. In addition, adiposity may increase levels of apo B-containing lipoproteins, decrease HDL and also be a source of inflammation [48, 49]. Our data support an inverse association between episodic inflammation and HDL levels among patients on dialysis, consistent with the possibility that decreases in HDL could mediate some of the increased cardiovascular risk observed in this population. Although the correlation between changes in apo A1 and α1AG was statistically significant, indicating that there is enough evidence in the data to demonstrate a non-zero correlation between them at the α = 0.05 level, the estimated $r^2$ was quite modest at 0.11 (corresponding to a correlation of 0.33). Thus, only an estimated 11% of the variability in changes in apo A1 was linked to changes in inflammation identified by changes in α1AG. Apo A1 levels as well as HDL levels are controlled by the activities of enzymes [cholesterol ester transfer protein (CETP), lecithin cholesterol acyltransferase protein (LCAT), the activity of the ATP binding cassette transporter (ABCA1)], as well as the rate of catabolism of HDL and of its constitutive apolipoproteins. These effects may not be directly associated with changes in inflammation. In the case of LCAT, some enzymes are suppressed in the presence of renal failure [50]. Activity of the ABCA1 cassette has anti-inflammatory effects in some tissues, and heterogeneity in the expression of this protein may therefore modify the effect of inflammation [40, 51]. Although CETP activity and mass are lower during acute inflammation [52], it would be incorrect to assert that all of the longitudinal variability in HDL or in its constitutive apolipoproteins is directly caused by the inflammatory response or that the quantitative effect of inflammation would be numerically identical in all individuals.

Acute inflammation in experimental models results in increased VLDL secretion accompanied by an increase in apo B [53, 54]. However, we did not find a change in apo B during episodes of inflammation [0.03 (95% CI −0.05 to 0.10) per 1 mg/dL change in α1AG]. Apo B does not appear to be functioning as an acute phase protein, and our data do not support inflammation as an explanation for the paradoxical association.
of high LDL with lower mortality. It has been hypothesized that the paradoxical association of high LDL with lower mortality could be related to suppression of LDL in the setting of inflammation and anorexia. However, our data do not support this hypothesis since apo B did not change significantly with changes in markers of inflammation (Figure 3). The direct relation between BMI and apo B is likely the result of increases in apo B containing lipoproteins associated with adiposity [55]; the inverse relation with creatinine may reflect a modification of this effect by representing that part of higher BMI is due to larger muscle mass [56]. These findings raise the possibility that body composition or nutritional status may be a more important mediator than inflammation of the association of lower LDL with higher mortality among patients on dialysis or that effects of inflammation on apolipoproteins are mediated by changes in body composition.

The apo B/A1 ratio has been found to be a stronger predictor of myocardial infarction and cardiovascular death than the ratio of total cholesterol to HDL cholesterol in persons with normal kidney function [22, 57, 58], and the apo B/A1 ratio may be more practical in the research setting because determinations are unaffected by whether samples are obtained in the fasting state [59]. The changes in the ratio of apo B/A1 that we observed were largely related to changes in apo A1, which themselves varied inversely with inflammation as observed here and reported by others [35–38].

This study has several strengths, including the relatively large sample size, national sampling frame and repeated measures of apolipoproteins and inflammatory markers. However, important limitations of our study should be acknowledged. First, we did not update information on weight or comorbidities after baseline assessment, which could lead to underestimation of associations with changes in apolipoproteins and which precluded us from assessing the extent to which changes in BMI are associated with changes in apolipoprotein concentrations. In addition, we did not make direct measures of body composition, instead using BMI and serum creatinine concentration as surrogates for adiposity and muscle mass, respectively, again potentially underestimating associations among body composition and apolipoproteins. Finally, while we adjusted for several important covariates in our multivariable analyses, we did not collect an infinite number of covariates in the CDS owing to its design; residual confounding could explain some of the associations described here. While the association between markers of inflammation and lipoprotein concentrations was modest, these findings do support a meaningful role of inflammation in determining the characteristic findings of dyslipidemia in the ESRD population.

In conclusion, we found that body composition was associated with apolipoprotein concentrations, with lower apo A1, higher apo B and a lower ratio of apo B/A1 among patients with higher BMI. Inflammatory markers were clearly associated with changes in apo A1 but not apo B levels over 1 year, suggesting that reduction in HDL cholesterol may be one mechanism by which inflammation confers higher cardiovascular risk among patients with ESRD and that, in contrast, apo B concentrations may be more closely related to nutritional status than to inflammation.

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

Joshua Zaritsky¹, Anjay Rastogi², George Fischmann², Jieshi Yan³, Kenneth Kleinman², Georgina Chow⁴, Barbara Gales⁴, Isidro B. Salusky⁴ and Katherine Wesseling-Perry⁴

¹Department of Pediatrics at Nemours/A.I. duPont Hospital for Children, Wilmington, DE, USA, ²Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, ³California Kidney Medical Group, Simi Valley, CA, USA and ⁴Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Correspondence and offprint requests to: Joshua Zaritsky; E-mail: joshua.zaritsky@nemours.org

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 Immutopics® 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