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Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis

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Abstract

Background—Fibroblast growth factor 23 (FGF-23) is a hormone that increases the rate of urinary excretion of phosphate and inhibits renal production of 1,25-dihydroxyvitamin D, thus helping to mitigate hyperphosphatemia in patients with kidney disease. Hyperphosphatemia and low 1,25-dihydroxyvitamin D levels are associated with mortality among patients with chronic kidney disease, but the effect of the level of FGF-23 on mortality is unknown.

Methods—We examined mortality according to serum phosphate levels in a prospective cohort of 10,044 patients who were beginning hemodialysis treatment and then analyzed FGF-23 levels and mortality in a nested case–control sample of 200 subjects who died and 200 who survived during the first year of hemodialysis treatment. We hypothesized that increased FGF-23 levels at the initiation of hemodialysis would be associated with increased mortality.

Results—Serum phosphate levels in the highest quartile (>5.5 mg per deciliter [1.8 mmol per liter]) were associated with a 20% increase in the multivariable adjusted risk of death, as compared with normal levels (3.5 to 4.5 mg per deciliter [1.1 to 1.4 mmol per liter]) (hazard ratio, 1.2; 95% confidence interval [CI], 1.1 to 1.4). Median C-terminal FGF-23 (cFGF-23) levels were significantly higher in case subjects than in controls (2260 vs. 1406 reference units per milliliter, P<0.001). Multivariable adjusted analyses showed that increasing FGF-23 levels were associated with a monotonically increasing risk of death when examined either on a continuous scale (odds ratio per unit increase in log-transformed cFGF-23 values, 1.8; 95% CI, 1.4 to 2.4) or in quartiles, with quartile 1 as the reference category (odds ratio for quartile 2, 1.6 [95% CI, 0.8 to 3.3]; for quartile 3, 4.5 [95% CI, 2.2 to 9.4]; and for quartile 4, 5.7 [95% CI, 2.6 to 12.6]).

Conclusions—Increased FGF-23 levels appear to be independently associated with mortality among patients who are beginning hemodialysis treatment. Future studies might investigate whether FGF-23 is a potential biomarker that can be used to guide strategies for the management of phosphorus balance in patients with chronic kidney disease.

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Dr. Jüppner reports holding an active patent on the C-terminal FGF-23 assay manufactured by Immutopics. Dr. Wolf reports having a pending patent application on FGF-23 measurements as a diagnostic aid and receiving consulting and lecture fees from Abbott, Genzyme, and INEOS and grant support from Shire. Dr. Thadhani reports receiving consulting and lecture fees from Abbott and Genzyme and grant support from Abbott. No other potential conflict of interest relevant to this article was reported.

Fibroblast growth factor 23 (FGF-23), a hormone that is secreted by osteoblasts, is an important regulator of phosphorus and vitamin D metabolism. It was first described as a pathogenic factor in rare hypophosphatemic syndromes in which "primary" increases in biologically active FGF-23 cause renal phosphate wasting, hypophosphatemia, inappropriately low levels of 1,25-dihydroxyvitamin D, and rickets or osteomalacia.[1-5] In contrast, depletion of FGF-23 leads to hyperphosphatemia, excessive levels of 1,25-dihydroxyvitamin D, ectopic calcification, and early death.[6-8] Subsequent studies highlighted the physiologic role of FGF-23 in maintaining normal serum phosphate levels despite variability in dietary phosphorus intake.[9,10]

In patients with kidney disease, normal serum phosphate levels are maintained despite a declining nephron mass, in part by progressive "secondary" increases in FGF-23 levels, which stimulate greater excretion of phosphate through the remaining nephrons and limit the absorption of dietary phosphorus by inhibiting the synthesis of 1,25-dihydroxyvitamin D.[11] Although increased levels of FGF-23 in patients with kidney disease are accompanied by certain features of primary excess of FGF-23, such as impaired bone mineralization and decreased 1,25-dihydroxyvitamin D levels,[12,13] kidney disease is also complicated by hyperphosphatemia, ectopic calcification, and premature death, which are associated with the depletion of FGF-23.[14,15] Thus, although increased serum phosphate levels and decreased 1,25-dihydroxyvitamin D levels are associated with increased mortality,[12,16] it is unknown whether compensatory increases in FGF-23 secretion lead to or provide protection against death. We performed a prospective study involving patients in whom hemodialysis was being initiated, in order to test the hypothesis that increased FGF-23 levels are associated with increased mortality independently of established risk factors and contemporaneous serum phosphate measurements.

Methods

Study Overview

The Accelerated Mortality on Renal Replacement (ArMORR) study is a prospective cohort study of 10,044 subjects who began hemodialysis treatment at any of the 1056 U.S. dialysis centers operated by Fresenius Medical Care North America (Waltham, MA) in 2004 or 2005. All the subjects underwent 1 year of follow-up except for those who died (15%), underwent kidney transplantation (3%), recovered renal function (4%), or transferred to a dialysis unit outside the Fresenius Medical Care North America system before completing 1 year of hemodialysis treatment (12%).

All clinical data were prospectively collected by clinicians at the point of care. These data included demographic characteristics of the subjects, coexisting conditions, results of studies performed by a central laboratory (Spectra East, Northvale, NJ), and outcomes. Plasma and serum samples that were obtained at the initiation of outpatient hemodialysis and that would otherwise have been discarded after routine clinical testing were saved and stored in liquid nitrogen. Since coexisting conditions were ascertained at the initiation of dialysis, the frequencies of certain conditions are lower in the ArMORR database than in federal registries, which use data collected up to 90 days after the initiation of dialysis. The study was approved by the institutional review board of the Massachusetts General Hospital, which waived the need for informed consent from each patient because all personal identifiers were removed from the blood samples and from the clinical data before transfer to the investigators (see the Supplementary Appendix, available with the full text of this article at http://www.nejm.org).

Study Population

We first examined mortality according to the baseline serum phosphate level in the entire ArMORR cohort and then analyzed the relation between the baseline FGF-23 level and mortality in a nested case–control sample, defining case subjects as those who died during the first year of hemodialysis treatment and controls as those who survived. On the basis of pilot data, we estimated that 50 case subjects and 50 controls would provide 90% power to detect a standardized difference of 0.66 in mean FGF-23 levels, assuming a two-sided type I error rate of 5%. Hyperphosphatemia is a risk factor for death[16] that is correlated with the FGF-23 level.[11] To minimize potential confounding effects of serum phosphate levels, we used frequency matching to randomly select 50 cases and 50 controls from the ArMORR cohort within each quartile of baseline serum phosphate levels. The final sample of 200 case subjects and 200 controls provided 90% power to detect an odds ratio for death of 1.8 for the highest FGF-23 quartile as compared with the lowest, with a two-sided type I error rate of 5%.

The main stimuli for the secretion of FGF-23 are increased dietary intake of phosphorus and activated vitamin D,[9,10,17] which has been associated with improved survival among patients undergoing hemodialysis.[18-21] Thus, increased FGF-23 levels in unselected patients could reflect high phosphorus exposure (a risk factor), previous therapy with activated vitamin D (a protective factor), or both. Therefore, we excluded subjects whose therapy with activated vitamin D was initiated before their baseline blood sample was obtained. Subjects remained eligible if they received activated vitamin D after the baseline measurements were obtained, and activated vitamin D was analyzed as a covariate. We excluded from the main analyses subjects who had less than 1 year of follow-up because they underwent kidney transplantation, recovered kidney function, or transferred to a dialysis center outside the Fresenius Medical Care North America system (19% of the subjects). To ensure that the 200 controls selected for the analysis were representative of all possible controls under the risk-set sampling theory, we measured FGF-23 levels in an additional random sample of 50 of the excluded subjects who were alive at the time the case subjects died.

Blacks and Hispanics are at a greater risk for end-stage renal disease than non-Hispanic whites but have a significant survival advantage when they begin undergoing dialysis.[22-25] Since there are no data on FGF-23 levels according to race or ethnic group or on the effect of FGF-23 levels on survival, we focused on black, Hispanic, and non-Hispanic white subjects and excluded subjects of other races (6%).

Exposures, Outcomes, and Covariates

The primary exposure variable was the baseline plasma FGF-23 level, measured at the initiation of outpatient hemodialysis. The primary outcome was 1-year, all-cause mortality. FGF-23 levels were measured in duplicate after a single freeze–thaw cycle in batched assays by an investigator who was unaware of the outcomes. Although C-terminal FGF-23 (cFGF-23) fragments accumulate in patients with kidney disease,[26] few studies of patients with renal failure have directly compared the results from cFGF-23 assays, which detect both intact FGF-23 (iFGF-23) and its C-terminal fragments, with iFGF-23 assays, which are specific for the intact molecule. Therefore, we measured both cFGF-23 and iFGF-23 (Immutopics) (interassay and intraassay coefficients of variation, <5% for each). Serum was available for radioimmunoassay of 1,25-dihydroxyvitamin D levels (DiaSorin) in 52 case subjects and 69 controls. Serum phosphate was measured with the use of standard assays, and 1-84 parathyroid hormone was measured with the use of a Nichols Bio-Intact assay.

Statistical Analysis

We used descriptive statistics to compare baseline demographic characteristics and the results of laboratory tests in the overall ArMORR cohort, among case subjects and controls, and according to race or ethnic group. We used a Spearman correlation analysis to test the association between cFGF-23 and iFGF-23. To test for nonlinear associations between FGF-23 and mortality, we examined FGF-23 levels in quartiles according to the distribution of values in the overall sample. We performed parallel analyses of cFGF-23 and iFGF-23.

We used a Cox proportional-hazards analysis to examine the risk of death associated with baseline phosphate levels in the full ArMORR cohort, censoring the data at the time a patient underwent kidney transplantation, transferred to a dialysis center outside the Fresenius Medical Care North America system, or recovered kidney function. We used logistic regression to test the association between FGF-23 levels and mortality in the case–control sample. Multivariable models were used to adjust for confounding. All analyses were prespecified except the post hoc analysis of the 50 additional controls. In the multivariable models, we adjusted for baseline laboratory values and the following case-mix variables: age, sex, race, ethnic group, cause of renal failure, blood pressure, body-mass index, coexisting conditions, vascular access at initiation of dialysis (fistula, graft, or catheter), urea reduction ratio, and facility-specific standardized mortality rates. We included variables in the multivariable models that in previous studies have been associated with the risk of death in people undergoing hemodialysis, as well as variables that differed significantly between case subjects and controls.

Results of laboratory tests were analyzed on a continuous scale; non-normal variables were log-transformed. Since treatment with dietary phosphorus binders can reduce FGF-23 levels,[27,28] we further adjusted for the use of phosphorus binders that preceded the FGF-23 measurements and conducted a prespecified subgroup analysis that excluded subjects who had received previous treatment with binders. We also adjusted for subsequent treatment with activated vitamin D. To test the robustness of the results with various analytic strategies, we examined models using forward, backward, and stepwise selection procedures; assessed goodness-of-fit with the use of the Hosmer–Lemeshow statistic; and tested for overfitting with the bootstrap technique. We formally tested for an interaction between the FGF-23 level and race or ethnic group by including interaction terms for black race and FGF-23 level and for Hispanic ethnic group and FGF-23 level, and when the results were significant, we analyzed stratified models. Analyses were performed with the use of Intercooled Stata software, version 7.0. Two-sided P values of less than 0.05, unadjusted for multiple testing, were considered to indicate statistical significance. All data were collected and analyzed by the ArMORR investigators.

Results

Serum Phosphate Levels and Mortality

The characteristics of the 10,044 ArMORR participants and the nested case–control sample at the initiation of hemodialysis are shown in Table 1. The mean (±SD) serum phosphate level, 4.6±1.6 mg per deciliter (1.49±0.52 mmol per liter), was lower than that in previous studies of patients undergoing hemodialysis; otherwise, baseline characteristics were similar to those in previous reports. After multivariable adjustment, serum phosphate levels greater than 5.5 mg per deciliter (highest quartile) were associated with an increased risk of death as compared with levels of 3.5 to 4.5 mg per deciliter (hazard ratio, 1.2; 95% confidence interval [CI], 1.1 to 1.4). This finding is consistent with the findings in previous studies.[20]

FGF-23 Levels and Mortality

There was a strong linear correlation between the cFGF-23 levels (median, 1752 reference units [RU] per milliliter; interquartile range, 1089 to 4019) and iFGF-23 levels (median, 713 pg per milliliter; interquartile range, 579 to 951) ($r = 0.74$, $P<0.001$) (Fig. 1 in the Supplementary Appendix). All subsequent results were qualitatively similar for cFGF-23 and iFGF-23; therefore, only the results for cFGF-23 are reported here (see the Supplementary Appendix for iFGF-23 results). Results of laboratory tests according to quartiles of cFGF-23 levels are shown in Table 2.

The median cFGF-23 level was significantly higher in patients who died than in those who survived, in the overall sample and within each quartile of serum phosphate levels except the highest, in which the comparison did not reach significance (Table 3). In univariate analyses, an increased cFGF-23 level was associated with an increased risk of death in the overall population (odds ratio per unit increase in the natural log-transformed cFGF-23 value, 1.5; 95% CI, 1.2 to 1.8) and in each serum phosphate quartile except the highest (Table 3) ($P = 0.26$ for an interaction). The FGF-23 level remained significantly associated with the risk of death when the analysis was adjusted for case-mix variables (odds ratio per unit increase in the log cFGF-23 value, 1.6; 95% CI, 1.2 to 1.9) and for results of laboratory tests (odds ratio per unit increase in the log cFGF-23 value, 1.8; 95% CI, 1.4 to 2.4). The results were qualitatively unchanged when different model-building strategies were used and when the models were further adjusted for the 1,25-dihydroxyvitamin D level, analyzed in categories, with a separate category for missing values, or when multiple imputation was used (data not shown). The final multivariable adjusted model was reliable ($P = 0.98$ by the Hosmer–Lemeshow test); evaluation with the bootstrap technique showed that the results were not overfitted to the data set.

When FGF-23 levels were examined in quartiles, there was a monotonic increase in mortality with increasing cFGF-23 levels in univariate, case-mix adjusted, and fully adjusted models (Fig. 1). In addition, the results were qualitatively unchanged when the analysis was further adjusted for subsequent therapy with activated vitamin D and for prior therapy with phosphorus binders and when subjects who had previously been treated with binders were excluded (data not shown), as well as in post hoc analyses that included the 50 additional controls (see the Supplementary Appendix).

Interaction with Race or Ethnic Group

Black and Hispanic patients had a significant survival advantage as compared with whites in the full ArMORR cohort and in the case–control sample (odds ratio for blacks, 0.5 [95% CI, 0.3 to 0.8], and odds ratio for Hispanics, 0.4 [95% CI, 0.2 to 0.7]); this finding is consistent with the results of previous studies involving patients undergoing hemodialysis.[12,24,25,29] Although there were no significant differences in phosphate levels according to race or ethnic group, the median FGF-23 level was significantly lower among blacks (1579 RU per milliliter; interquartile range, 966 to 2959) and Hispanics (1336 RU per milliliter; interquartile range, 1094 to 2262), than among whites (2016 RU per milliliter; interquartile range, 1132 to 4865) ($P = 0.02$ and $P = 0.04$, respectively). Although there was no significant interaction among ethnic group, FGF-23 levels, and mortality, there was a significant interaction with race ($P = 0.048$). As compared with whites who had cFGF-23 levels below the population median, blacks who had cFGF-23 levels below the median had a 60% lower risk of death (odds ratio, 0.4; 95% CI, 0.2 to 0.7), whereas the risk of death was similar for blacks and whites who had cFGF-23 levels above the median (odds ratio, 1.3 [95% CI, 0.7 to 2.3] and 1.6 [95% CI, 0.97 to 2.5], respectively).

Discussion

In this prospective study of patients who were beginning hemodialysis treatment, increased FGF-23 levels were associated with mortality independently of serum phosphate levels and other known risk factors. The results were virtually identical with the use of two different FGF-23 assays and showed a strong dose–response relationship. The magnitude of the risk associated with increasing FGF-23 quartiles was substantially larger than the analogous results for serum phosphate quartiles in the overall cohort. In addition, differences according to race were apparent. Further studies are needed to determine whether strategies for the control of phosphorus homeostasis that are guided by FGF-23 measurements might benefit patients with kidney disease who have normal serum phosphate levels — patients for whom these therapies are not routinely recommended but for whom they may be of substantial clinical benefit.

Patients with renal failure have severe vascular disease and are at risk for premature death in association with hyperphosphatemia and 1,25-dihydroxyvitamin D deficiency,[12] but several observational studies suggest that for patients who are undergoing hemodialysis, therapy with activated vitamin D provides a survival benefit that is independent of the serum phosphate level.[18-21] FGF-23–knockout mice are characterized by hyperphosphatemia, 1,25-dihydroxyvitamin D intoxication, and metastatic vascular calcification, resulting in early death. These phenotypic features of FGF-23–knockout mice can be attenuated by ablation of 25-hydroxyvitamin D-1α-hydroxylase, suggesting that excessive 1,25-dihydroxyvitamin D levels in combination with hyperphosphatemia may be harmful.[30] Indeed, the maintenance of FGF-23–knockout mice on a diet deficient in vitamin D prolongs their survival despite persistent hyperphosphatemia.[8] Thus, whereas the depletion of FGF-23 and an excess of 1,25-dihydroxyvitamin D are associated with increased mortality in the relevant animal models with normal renal function, an excess of FGF-23 and a deficiency of 1,25-dihydroxyvitamin D appear to be associated with increased mortality in humans with renal failure. These discrepant results highlight the need for carefully designed studies in humans with kidney disease. We aimed to minimize confounding by excluding patients who had previously been treated with activated vitamin D. Although this limits our ability to generalize the results to all patients who are undergoing hemodialysis, it would be inappropriate to cite the present study as evidence of the potential toxicity of activated vitamin D through increased FGF-23 levels.

Previous studies of FGF-23 were conducted among mostly white and Asian populations.[9-11,26,31] None of those studies compared levels across races, and none reported levels among blacks and Hispanics. We found that FGF-23 levels were 22% and 34% lower in blacks and Hispanics, respectively, than in whites. This finding is not surprising when it is interpreted in the context of other racial differences in mineral metabolism. For example, blacks have decreased urinary phosphate excretion and increased serum phosphate levels as compared with whites, despite increased parathyroid hormone levels.[32-34] Decreased FGF-23 expression could account for this discrepancy. Along with increased parathyroid hormone levels, decreased FGF-23 levels could also account for higher 1,25-dihydroxyvitamin D levels among blacks than among whites, despite the fact that blacks have lower levels of 25-dihydroxyvitamin D, which is the metabolic precursor of 1,25-dihydroxyvitamin D.[32] One might speculate that decreased FGF-23 levels among blacks could represent an adaptation to maintain normal bone mineralization in the face of high rates of vitamin D deficiency and secondary hyperparathyroidism. The question of whether decreased FGF-23 levels might contribute to the well-known but poorly understood survival advantage of blacks who are undergoing dialysis is also intriguing. Support for this possibility is provided by our findings that blacks had significantly lower FGF-23 levels

than whites and that among subjects with lower FGF-23 levels, blacks had a significantly decreased risk of death as compared with whites.

A limitation of this study is that we were unable to determine whether increased FGF-23 levels are directly toxic or are a surrogate marker of the toxicity of other factors. It is possible that at the extremely high concentrations we observed, FGF-23 binds FGF receptors with sufficiently high affinity, even in the absence of its coreceptor Klotho, to stimulate the production of factors that have been implicated in the development of vascular disease but that are normally generated in response to basic FGF.[35] Alternatively, increased FGF-23 levels may reflect toxicity that is due to prolonged exposure to a high dietary intake of phosphorus, which has been associated with adverse outcomes in patients with kidney disease but which we were unable to quantify in this study. Additional research is needed to explore these possibilities. Other potential limitations include residual confounding by coexisting conditions that were not ascertained, misclassification of vitamin D treatment, and the restriction to 1-year outcomes.

The 20% increased risk of death that we observed among patients in the highest quartile of phosphate levels was similar to the risk in previous reports.[16] Similarly, serum phosphate levels greater than 3.5 mg per deciliter were associated with approximately a 28% increase in the risk of death in studies involving patients with early stages of kidney disease or patients without kidney disease.[36,37] In contrast, we found a monotonic, dose–response relationship between FGF-23 levels and mortality, such that subjects in the highest quartile of FGF-23 levels had nearly a 600% increase in risk as compared with subjects in the lowest quartile. These results suggest that serum phosphate levels, which are influenced by dietary intake, phosphorus binders, urinary and dialysis clearance, and bone and soft-tissue deposition, provide only a partial assessment of the risk associated with abnormal phosphorus metabolism, especially when the levels are normal. In comparison, FGF-23 levels were most informative when serum phosphate levels were relatively low. Thus, FGF-23 could represent a new biomarker for assessing the risk of death that may be especially useful in patients with early kidney disease, in whom FGF-23 levels increase long before hyperphosphatemia first develops[11] but who already have a markedly increased risk of death.[38] Currently, the vast majority of the estimated 20 million people with chronic kidney disease in the United States are neither advised to restrict dietary phosphorus nor treated with dietary phosphorus binders, which lower FGF-23 levels in a dose–response fashion.[9,10,27,28] The results of the current study suggest that FGF-23 measurements may be a sensitive tool to identify which of those patients who have normal serum phosphate levels might benefit from the use of such strategies to manage phosphorus balance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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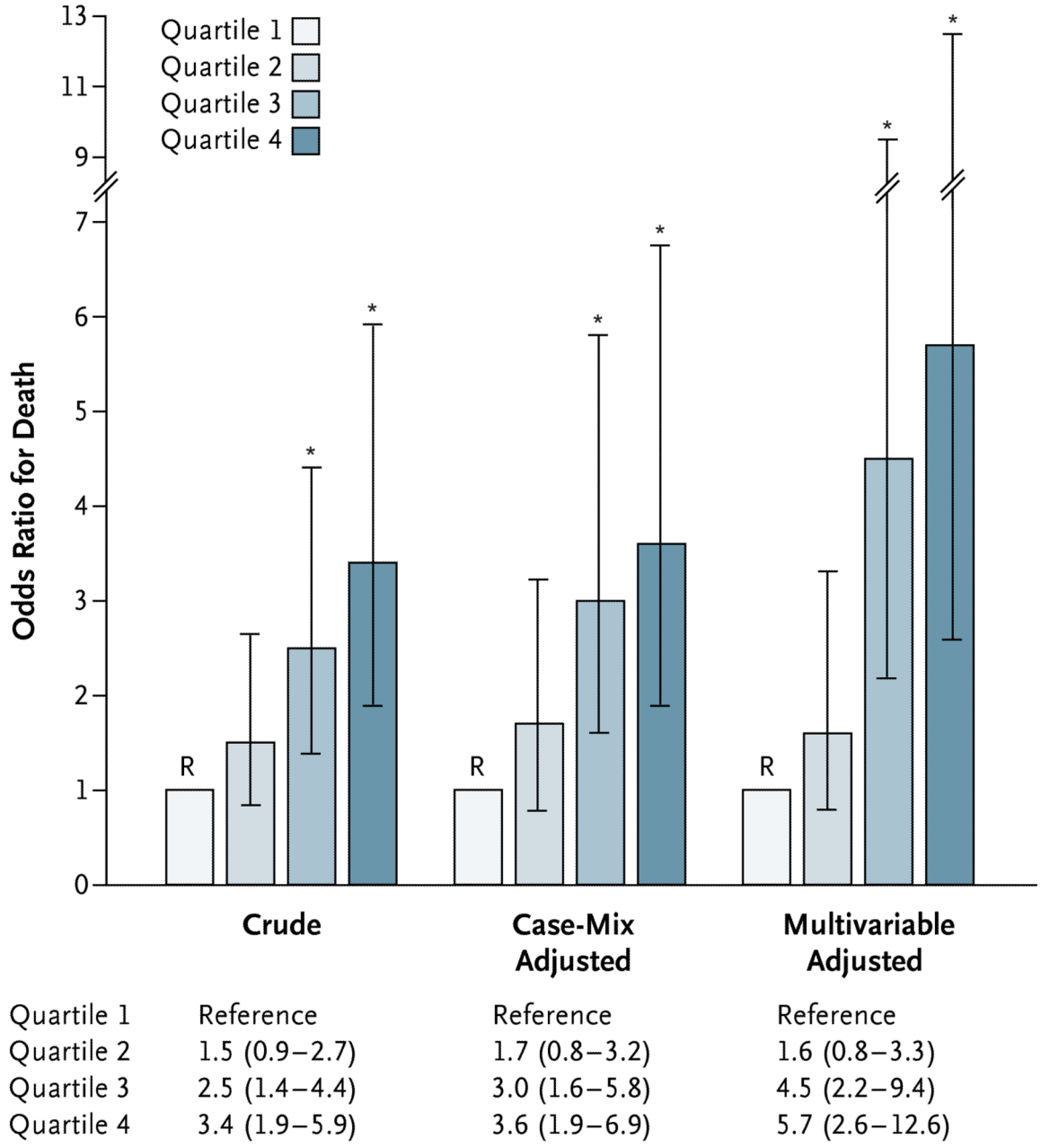

	Crude	Case-Mix Adjusted	Multivariable Adjusted
Quartile 1	Reference	Reference	Reference
Quartile 2	1.5 (0.9–2.7)	1.7 (0.8–3.2)	1.6 (0.8–3.3)
Quartile 3	2.5 (1.4–4.4)	3.0 (1.6–5.8)	4.5 (2.2–9.4)
Quartile 4	3.4 (1.9–5.9)	3.6 (1.9–6.9)	5.7 (2.6–12.6)

Figure 1. Odds Ratios (and 95% CIs) for Death According to Quartile of C-Terminal Fibroblast Growth Factor 23 (cFGF-23) Levels

Crude, case-mix adjusted, and multivariable adjusted odds ratios for death are shown according to quartile of cFGF-23 levels (quartile 1, <1090 reference units [RU] per milliliter; quartile 2, 1090 to 1750 RU per milliliter; quartile 3, 1751 to 4010 RU per milliliter; quartile 4, >4010 RU per milliliter). The case-mix adjusted analysis included the following variables: age, sex, race or ethnic group, blood pressure, body-mass index, facility-specific standardized mortality rate, vascular access at initiation of dialysis (fistula, graft, or catheter), cause of renal failure, urea reduction ratio, and coexisting conditions. The multivariable adjusted analysis included the case-mix variables plus phosphate, calcium, log parathyroid hormone, albumin, creatinine, and ferritin levels. Quartile 1 was the reference

group in all models. I bars represent 95% confidence intervals. Asterisks indicate P<0.05. R denotes reference.

Table 1

Characteristics of the ArMORR Cohort and the Nested Case–Control Sample at the Initiation of Hemodialysis.*

Characteristic	Full Cohort (N = 10,044)	Patients Who Died (N = 200)	Patients Who Survived (N = 200)	P Value
Age (yr)	63±16	70±14	61±15	<0.001
Female sex (%)	45	47	46	0.76
Black race (%)†	32	24	36	0.01
Hispanic ethnicity (%)†	13	7	15	0.02
Body-mass index‡	28±9	26±8	28±6	0.02
Blood pressure (mm Hg)				
Systolic	148±21	140±27	146±21	0.006
Diastolic	74±14	70±16	76±13	<0.001
Cause of renal failure (%)				
Diabetes	43	42	44	0.69
Hypertension	35	40	37	0.61
Glomerulonephritis	10	6	11	0.05
Other	12	14	9	0.56
Initial vascular access (%)				
Fistula	26	14	36	<0.001
Graft	11	10	11	0.74
Catheter	63	76	53	<0.001
Coexisting conditions (%)				
Coronary artery disease	10	14	8	0.80
Congestive heart failure	12	21	10	0.001
Cancer	3	6	3	0.08
Stroke	3	6	4	0.33
Laboratory tests				
Albumin (g/dl)	3.5±0.5	3.2±0.5	3.4±0.6	<0.001
Calcium (mg/dl)	8.9±0.8	8.4±0.8	8.3±0.9	0.15
Phosphate (mg/dl)	4.6±1.6	4.4±1.7	4.4±1.6	0.98
Parathyroid hormone (pg/ml)				0.36
Median	206	192	198	
Interquartile range	111–352	101–326	113–343	
Alkaline phosphatase (U/liter)				0.77
Median	83	86	89	
Interquartile range	64–112	68–126	68–112	
Creatinine (mg/dl)	6.3±2.7	5.4±2.3	6.3±2.6	<0.001
Hemoglobin (g/dl)	10.3±1.4	10.1±1.3	10.2±1.3	0.56
Ferritin (ng/ml)				0.05

Characteristic	Full Cohort (N = 10,044)	Patients Who Died (N = 200)	Patients Who Survived (N = 200)	P Value
Median	202	218	199	
Interquartile range	98–398	94–480	88–332	
Urea reduction ratio (%)	68±11	69±11	69±11	0.56

* Plus–minus values are means ±SD. P values are for the comparisons between patients who died and those who survived. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for phosphate to millimoles per liter, multiply by 0.3229. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

† Race and ethnic group were self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2

Laboratory Results and Use or Nonuse of Phosphorus Binders, According to Quartiles of cFGF-23 Level.*

Variable	cFGF-23 Quartile 1 (<1090 RU/ml)	cFGF-23 Quartile 2 (1090–1750 RU/ml)	cFGF-23 Quartile 3 (1751–4010 RU/ml)	cFGF-23 Quartile 4 (>4010 RU/ml)	P Value
Albumin (g/dl)	3.4±0.5	3.3±0.5	3.3±0.6	3.3±0.5	0.13
Creatinine (mg/dl)	5.3±2.2	5.4±2.2	6.3±2.2	6.6±2.9	<0.001
Phosphate (mg/dl)	3.9±1.2	4.1±1.3	4.5±1.6	5.2±2.1	<0.001
Calcium (mg/dl)	8.8±0.8	8.9±0.7	8.8±0.8	9.0±0.8	0.15
Parathyroid hormone (pg/ml)	180 (99–313)	137 (95–273)	253 (119–377)	234 (145–435)	0.22
Alkaline phosphatase (U/liter)	82 (64–103)	89 (67–114)	91 (69–114)	100 (77–131)	<0.001
1,25-Dihydroxyvitamin D (pg/ml)†	9.1±5.2	6.9±6.0	8.4±5.0	7.5±5.8	0.45
Phosphorus binders (% of patients)	12	8	9	6	0.18

* Plus–minus values are means ±SD. P values are for linear trend. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for phosphate to millimoles per liter, multiply by 0.3229. To convert the values for calcium to millimoles per liter, multiply by 0.250. cFGF-23 denotes C-terminal fibroblast growth factor 23, and RU reference units.

† Data on 1,25-dihydroxyvitamin D levels were available for 121 patients.

Table 3

Levels of cFGF-23 and Associated Risk of Death within Serum Phosphate Quartiles in the Case–Control Sample.

Phosphate Level	Median cFGF-23 Level (interquartile range)		P Value	Odds Ratio for Death (95% CI)*
	Patients Who Died (N = 200)	Patients Who Survived (N = 200)		
	reference units per milliliter			
All levels	2260 (1196–5296)	1406 (989–2741)	<0.001	1.5 (1.2–1.8)
<3.5 mg/dl	1790 (1175–3941)	1148 (927–2169)	0.008	1.8 (1.2–2.8)
3.5–4.4 mg/dl	2049 (1109–4865)	1131 (893–1629)	0.003	1.8 (1.2–2.7)
4.5–5.5 mg/dl	2207 (1186–5238)	1499 (1044–2262)	0.02	1.8 (1.1–3.0)
>5.5 mg/dl	3541 (1871–10,491)	2686 (1527–6210)	0.29	1.1 (0.7–1.6)

* The odds ratios are for a one-unit increase in the natural log-transformed cFGF-23 level in all 400 patients and in each quartile of 100 patients.