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**Markers of Mineral Metabolism and Vascular Access Complications: The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study**

**Running Title: Mineral Metabolism and Vascular Access**

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None of the authors have any conflict of interest.

**Key Words:**

Vascular Access, Vitamin D25, FGF-23, PTH, Mineral metabolism.

**Abstract**

**Introduction:** Vascular access dysfunction is a major cause of morbidity in patients with end stage renal disease (ESRD) on chronic hemodialysis. The effects of abnormalities in mineral metabolism on vascular access is unclear. In this study, we evaluated the association of mineral metabolites, including 25-hydroxy vitamin D (25(OH)D) and fibroblast growth factor-23 (FGF-23), with vascular access complications.

**Methods:** We included participants from the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study who were using an arteriovenous fistula (AVF; n=103) or arteriovenous graft (AVG; n=116). Serum levels of 25(OH)D, FGF-23, Parathyroid Hormone (PTH), calcium, phosphorus, C-reactive protein (CRP) and interleukin-6 (IL-6) were assessed from stored samples. Participants were followed for up to one year or until a vascular access intervention or replacement.

**Results:** A total of 24 participants using an AVF and 43 participants using an AVG experienced access intervention. Those with 25(OH)D level in the lowest tertile (<11 ng/ml) had an increased

risk of AVF intervention compared to those with higher 25(OH)D levels (adjusted relative hazard [aHR] = 3.28; 95% confidence interval [CI]: 1.31, 8.20). The highest tertile of FGF-23 (>3750 RU/ml) was associated with greater risk of AVF intervention (aHR=2.56; 95% CI: 1.06, 6.18). Higher PTH was associated with higher risk of AVF intervention (aHR=1.64 per standard deviation of log(PTH); 95% CI: 1.02, 2.62). These associations were not observed in participants using an AVG. None of the other analytes were significantly associated with AVF or AVG intervention.

**Conclusion:** Low levels of 25(OH)D and high levels of FGF-23 and PTH are associated with increased risk of AVF intervention. Abnormalities in mineral metabolism are risk factors for vascular access dysfunction and potential therapeutic targets to improve outcomes.

**Introduction**

Maintaining patent vascular access is essential for patients with end-stage renal disease (ESRD) on hemodialysis (HD) to prevent life-threatening technique failure. Access complications result in a high burden of hospital admissions, procedures and costs for patients on HD. [1,2] The pathophysiologic mechanisms underlying vascular access complications are poorly understood. Discovery of potential predictors and subsequent targets for intervention could help design new preventive strategies. Our prior work suggests mineral metabolism may be an important target for intervention but confirmatory studies are needed. [3]

Abnormalities in mineral homeostasis are common in patients with ESRD and are associated with numerous adverse outcomes including vascular calcification, inflammation and

mortality.[4-8] Impaired excretion of phosphorus due to low kidney function raises fibroblast growth factor 23 (FGF23). FGF23 decreases conversion of 25-hydroxy vitamin D (25(OH)D) to its active 1,25 D form, causing calcium to fall and parathyroid hormone (PTH) to rise. This complex interplay of factors may promote vascular disease through multiple pathways including calcification, endothelial dysfunction, inflammation, activation of the renin-angiotensin-aldosterone system and others. [9]

Deficiency of 25(OH)D is common among patients with ESRD, with some studies estimating the prevalence above 80%. [10] Due to the block in conversion from 25(OH)D to active 1,25D in ESRD, 1,25D or its analogs are frequently administered to patients with ESRD to overcome these adverse effects. Nonetheless, 25(OH)D may be locally converted in tissues or have other direct effects, and recent studies suggest that low 25(OH)D associates with mortality in HD patients in meta-analyses.[11] Vitamin D deficiency has been associated with hypertension, insulin resistance, viral and bacterial infection risk, and multiple organ damage due to systemic inflammation.[12] Despite consistent associations of disordered mineral homeostasis and vascular outcomes in ESRD, few studies have investigated the role of these factors in vascular access outcomes.

The aim of the study was to determine the association of markers of mineral metabolism with vascular access outcomes. We hypothesized that lower levels of 25(OH)D and higher levels of fibroblast growth factor 23 (FGF23), serum calcium, phosphorus, parathyroid hormone (PTH) and markers of inflammation are associated with greater incidence of vascular access

complications. We also hypothesized that these associations are present for both AV fistulae and AV grafts, but stronger in AV fistulae.

## **Methods**

### *Study Design and Population*

Study participants were dialysis patients who participated in the CHOICE (Choices for Healthy Outcomes in Caring for ESRD) Study. [13] CHOICE was a national, prospective cohort study of 1,041 incident dialysis patients initiated in 1995 to investigate treatment choices of modality and dose, and outcomes of dialysis care. Inclusion criteria for CHOICE were the initiation of chronic outpatient dialysis within the past 6 months, ability to provide informed consent for participation, age older than 17 years, and ability to speak English or Spanish. All patients provided informed consent. Patients were enrolled a median of 45 days after initiation of chronic dialysis (98% within 4 months) from sites across the country affiliated with DCI. This analysis is limited to the CHOICE participants who used HD as their initial renal replacement modality (n = 762), were enrolled at clinics associated with Dialysis Clinic Inc. (DCI; n = 735), had samples available in the DCI specimen bank (n=501), and were using their initial permanent access at the time of the blood draw for analysis (n=219).

### *Data Collection*

Non-fasting pre-dialysis blood specimens were centrifuged at 2,500 to 3,000 rpm for 15 minutes within 30 to 45 minutes of blood collection. [5] Separated and refrigerated specimens then were mailed overnight on ice to the DCI Central Laboratory until they were thawed (1 thaw cycle) for analysis. Each blood collection was aliquoted into multiple vials and stored at  $-80^{\circ}\text{C}$ . Serum calcium, phosphorus, PTH and total alkaline phosphatase were calculated as the average of all clinical measurements performed during routine dialysis care up to 4.5 months after enrollment to correspond to the time when FGF23 and 25(OH)D were measured. PTH was measured on a total of 166 patients using the Diasorin intact assay (Diasorin, Inc., Stillwater, MN, USA). C-terminal FGF23 (Immutopics, San Clemente, CA, USA) and 25(OH)D (Immunodiagnostic Systems, Scottsdale, AZ, USA) were measured at a single time-point in stored plasma samples drawn within 6 months of enrollment (median of 90 days).

Other characteristics assessed at initiation of dialysis included age, gender, race (self-reported, categorized as African-American or other), BMI, and comorbidity. Comorbidity was assessed at baseline using the Index of Coexistent Disease (ICED), which is a validated 4-level scale of comorbidity that incorporates measures of both disease severity and physical impairment. The ICED scores were categorized as mild (0 or 1), moderate (2), or severe (3). [14, 15]

Vascular access information was obtained through review of discharge summaries, dialysis flow sheets, and dialysis clinic progress notes. The first and last date of use for each access was recorded. The primary outcome was any access-related intervention, including



angioplasty, thrombolysis, surgical revision of a poorly functioning or nonfunctioning fistula or graft and dialysis catheter placement. Follow-up was censored on the date of access intervention, 1 year follow-up, or at the time of death, whichever came first.

### *Statistical Analysis*

Baseline characteristics of the study population were described and compared across levels of 25(OH)D and FGF-23 using linear or logistic regression, as appropriate. We grouped the upper two tertiles of 25(OH)D and the lower two tertiles of FGF-23 for comparison to the remaining tertile. Unadjusted survival was compared across tertiles of each biomarker using Kaplan–Meier curves and log-rank tests. Independent associations were estimated by Cox proportional hazards models. Analyses were repeated in the subset of patients with PTH measurements available (n=166). Continuous associations between 25(OH)D, FGF-23 and PTH with the incidence rate ratio of AVF intervention or failure were assessed with restricted cubic spline Poisson models, using 3 knots at the 10<sup>th</sup>, 50<sup>th</sup> and 90<sup>th</sup> percentiles. Statistical analyses were performed using Stata (Special Edition, version 13; Stata Corporation, College Station, TX, USA).

### **Results**

A total of 219 patients had complete information and were receiving hemodialysis through a working AVF (n=103) or AVG (n=116) at the time of the blood draw and are included in these analyses. These participants did not differ from the remaining 543 hemodialysis patients in terms of age, race, sex, BMI or severity of comorbidities (all  $p>0.32$ ).

Those with higher 25(OH)D were more likely to be female and less likely to be obese than their counterparts with lower 25(OH)D. (Table 1) As expected, serum calcium was significantly correlated with both 25(OH)D ( $r=0.28$ ;  $p<0.001$ ) and FGF23 ( $r=0.18$ ;  $p=0.007$ ) (Table2). Serum phosphorus also was strongly correlated with FGF-23 ( $r=0.43$ ;  $p<0.001$ ). 25(OH)D and FGF23, however, were not significantly correlated ( $r=0.11$ ;  $p=0.11$ ). CRP and IL-6 were strongly correlated ( $r=0.55$ ;  $p<0.001$ ) as expected, and calcium was negatively correlated with both CRP ( $r=-0.07$ ) and IL-6 ( $r=-0.16$ ;  $p=0.02$ ).

#### *Associations with Arteriovenous Fistula Intervention or Failure*

A total of 103 patients were using an AVF at the time of the blood draw (Table 3). Among these, 24 experienced AVF interventions. A 25(OH)D level in the lowest tertile ( $< 11$  ng/ml) was associated with a higher incidence of AVF intervention than higher levels in unadjusted analyses (relative hazard [RH] = 2.50; 95% confidence interval [CI]: 1.12,5.60) (Figure 1) This association was statistically significant after adjustment for age, race, gender, BMI, and ICED (RH = 2.74; 95% CI: 1.13,6.64).(Figure 2). The association between 25(OH)D

and AVF intervention was curvilinear, with greater risk observed at 25(OH)D levels below approximately 6 ng/mL (Figure 2). Those with an FGF-23 level in the highest tertile (>3750 RU/ml) had a marginally higher risk of AVF intervention (adjusted RH = 2.15; 95% CI: 0.90,5.15) though it was not statistically significant. (Table 1. Figure 3, 4). This association remained non-significant even after adjusting for phosphorus levels. (Table 3). Among the other markers of mineral metabolism and inflammation, only PTH was significantly associated with AVF intervention in unadjusted and adjusted analyses (adjusted RH 1.67; 95% CI: 1.00, 2.78) (Table 4).

In a model including 25(OH)D and FGF23, both low 25(OH)D and high FGF23 were significantly associated with AVF intervention (Table 5). These associations were also independent of PTH in analyses limited to the subset of patients with PTH assessed (Table 5). Higher PTH also remained significantly associated with AVF intervention in models adjusted for 25(OH)D and FGF23 (Figure 5).

#### *Associations with Arteriovenous Graft intervention or Failure*

A total of 43 of the 116 patients using an AVG experienced access intervention (Table 6). Neither 25(OH)D nor FGF23 were significantly associated with AVG intervention in unadjusted or adjusted analyses. Additionally, none of the markers tested were significantly associated with AVG intervention.

## Discussion

Mineral metabolism disorders have been associated with many adverse outcomes in ESRD, including cardiovascular disease and mortality. [4,16] Few studies heretofore have investigated the relationship of markers of mineral metabolism with vascular access failure. In a cohort of 128 patients, Walker, et al found 25(OH)D deficiency (<20 ng/ml) to be associated with higher incidence of vascular access failure defined as thrombosis or abandonment for non-maturation or loss of patency.[17] However, they did not study other factors, such as FGF23 and PTH. Morena et al followed 128 patients with AVF for up to 2 years. Thrombosis occurred in 19 patients and those with AVF thrombosis had higher levels of phosphorus compared to those without AVF dysfunction [18]. This study did not find any association of serum CRP level with risk of vascular access complications, similar to our findings. The association of 25(OH)D and FGF23 levels with vascular access complications were not studied. We measured both the separate and combined effect of these analytes on AVF and AVG complications. We found that low 25(OH)D and high FGF23 level are both independently associated with increased risk of AVF intervention, but not with AVG intervention.

Deficiency of 25(OH)D has been associated with many pathophysiologic processes, including generalized inflammation, endothelial dysfunction, left ventricular hypertrophy and increased predisposition to infections. [19] Production of FGF23 is regulated in part by 1,25 DiHydroxy Vitamin D. [20] FGF23 binds to FGF receptor and  $\alpha$  Klotho complexes to stimulate

renal phosphate excretion, increased PTH production and suppress activated vitamin D levels. [21]

One potential pathophysiologic mechanism through which abnormal levels of 25(OH)D and FGF23 may lead to vascular access complications is through generalized inflammation. Cholecalciferol replacement in ESRD patients has been shown to decrease the level of inflammatory markers. [22] Although we did not find any association between higher levels of IL-6 and CRP with AVF failure, other inflammatory pathways may be responsible for the associations we observed. Apart from IL-6, studies have identified increased levels of tumor necrosis factor alpha (TNF alpha) [23] and IL-8[24] in ESRD population and these have been associated with increased risk of cardiovascular complications, including atherosclerosis. [25] Furthermore, vitamin D may also regulate the renin angiotensin aldosterone (RAAS), or promote endothelial function through additional pathways. [26, 27] FGF23 may promote vascular access dysfunction indirectly, through its physiologic role in decreasing the levels of 1,25 Dihydroxy Vitamin D. [28] It may also work directly by increasing the inflammatory markers like lipocalin-2, TNF alpha and transforming growth factor beta (TGF Beta) as shown in animal models. [29] We did not find any increased risk of these abnormalities on loss of AVG patency indicating that they might not have a similar effect on anastomosis with synthetic surfaces as they have on native veins.

The cut-off values for 25(OH)D and FGF-23 analysis are based on tertiles of their distributions and validated by the continuous associations shown in figure 1 and 3, respectively.

The cut-off for 25(OH)D in our study is lower than <20 ng/ml used in some other analyses. Our findings suggest that higher risk associated with 25(OH)D deficiency may be limited to those that have severely decreased levels. This has potential implications for trials designed to look at the effect of vitamin D replacement as only this group with very low levels might benefit from intervention. Indeed, in a small trial looking at the efficacy of high dose Vitamin D3 replacement in improving AVF maturation, 25(OH)D level of < 30 ng/ml was used as inclusion criteria and the mean serum 25(OH)D was 16.8 ng/ml. [30] This study failed to show a benefit of D3 replacement. Future studies might examine the impact in those with even lower 25(OH)D levels.

High PTH level was associated with a higher risk of AVF failure with the association being stronger when adjusted for 25(OH)D and FGF-23. Levels of PTH were available for only a subset of patients, which limits the precision of our estimates. Secondary hyperparathyroidism has been implicated in vascular calcification and increased cardiovascular mortality in ESRD population. [31] It can exert its effect on vasculature by impairing lipid metabolism, insulin resistance, activation of vascular smooth muscle cells and increase calcium and phosphorus deposition. [32]

Our study is limited by the observational design which precludes determination of causality. The relatively small number of events limits the precision of our estimates. Another limitation is the exclusion of patients with a nonfunctioning access, which may have introduced a selection bias. This group with primary access failure might have had a different effect of mineral metabolism disorders compared to the group included in the study.

Although far from definitive, this study suggests several potential therapeutic targets to improve vascular access outcomes that should be studied more rigorously. A recent pilot study found increased patency of dialysis access with direct injection of calcitriol to the stenosis lesion after balloon angioplasty. [33] On the other hand, another small trial failed to show any benefit of cholecalciferol replacement on vascular access patency. [30] Larger, prospective clinical trials with interventions to control multiple aspects of bone mineral metabolism should be designed to study the effect of these potential therapeutic targets on vascular access outcomes.

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**Table 1. Baseline characteristics, by 25(OH)D and FGF-23 category\***

	25(OH)D			FGF-23		
	Tertile 1 (<11 ng/mL)	Tertile 2-3 (≥11 ng/mL)	P	Tertile 1-2 (<3,750 RU/mL)	Tertile 3 (≥3,750 RU/mL)	P
N	74	145	-	145	74	-
Age, years	59.6 (11.5)	58.2 (15.9)	0.48	60.2 (14.4)	55.7 (14.4)	0.03
Female, %	36.5	59.2	0.002	50.3	54.1	0.60
Black, %	35.1	30.3	0.47	35.2	25.7	0.16
ICED	2.0 (0.8)	1.9 (0.8)	0.38	1.9 (0.8)	2.0 (0.8)	0.75
Body Mass Index, kg/m <sup>2</sup>	30.1 (7.3)	26.4 (5.8)	<0.001	27.4 (6.4)	28.2 (6.9)	0.43
25(OH)D, ng/mL	8.8 (1.5)	17.3 (5.4)	-	14.2 (5.5)	15.1 (6.9)	0.29

FGF-23, RU/mL	3581 (4398)	4713 (5099)	0.11	1,392 (923)	10,088 (4365)	-
Calcium, mg/dl	9.0 (0.6)	9.3 (0.7)	0.006	9.1 (0.6)	9.3 (0.7)	0.08
Phosphorus, mg/dl	5.2 (1.2)	5.4 (1.3)	0.18	5.0 (1.1)	6.0 (1.2)	<0.001
iPTH, pg/ml	222 (172)	290 (415)	0.22	228 (323)	333 (365)	0.06
CRP, mg/dl	1.0 (1.5)	0.7 (1.0)	0.03	0.7 (1.1)	0.9 (1.3)	0.43
IL-6, mg/dl	8.9 (15.9)	6.3 (9.9)	0.13	7.0 (12.1)	7.5 (12.7)	0.77
Arteriovenous Fistula, %	40.1	50.3	0.17	43.4	54.1	0.14

\* baseline characteristics (unadjusted = bivariable)

ICED: Index of Co-Existent Diseases; iPTH: Intact parathyroid hormone (n=166)

**Table 2. Correlations between markers of mineral metabolism and inflammation\***

	25(OH)D	FGF-23	Calcium	Phosphorus	iPTH (n=166)	CRP
FGF-23	0.11	-	-	-	-	-

Calcium	<b>0.28</b> ( <b>&lt;0.001</b> )	<b>0.18</b> ( <b>0.007</b> )	-	-	-	-
Phosphorus	0.07	<b>0.43</b> ( <b>&lt;0.001</b> )	0.02	-	-	-
iPTH (n=166)	-0.07	0.12	<b>-0.31</b> ( <b>&lt;0.001</b> )	0.16	-	-
CRP	-0.08	0.07	-0.07	-0.01	-0.02	-
IL-6	-0.07	0.11	<b>-0.16</b> ( <b>0.02</b> )	0.01	0.10	<b>0.55</b> ( <b>&lt;0.001</b> )

\*Correlations based on Unadjusted Log Values of each marker.

25(OH)D: 25-hydroxy vitamin D; FGF-23: Fibroblast growth factor-23; iPTH: intact parathyroid hormone; CRP: C-reactive protein; IL-6: interleukin-6.

**Table 3. Incidence of Arteriovenous Fistula Intervention, by 25(OH)D and FGF-23 category\***

	25(OH)D		FGF-23	
	Tertile 1 (<11.0 ng/mL)	Tertile 2-3 (≥11 ng/mL)	Tertile 1-2 (<9,750 RU/mL)	Tertile 3 (≥3,750 RU/mL)
Events / N	11/30	13/73	12/63	12/40
Incidence Rate (per 100 person-months)	5.34	2.05	2.19	4.14
Unadjusted Relative Hazard	2.50 (1.12, 5.60)	Reference	Reference	1.76 (0.79, 3.93)
Adjusted# Relative Hazard	2.74 (1.13, 6.64)	Reference	Reference	2.15 (0.90, 5.15)
Unadjusted + Log Phosphorus	2.90 (1.22, 6.92) P=0.02	Reference	Reference	2.22 (0.81, 6.09) P=0.12
Adjusted# + Log Phosphorus	3.38 (1.30, 8.80) P=0.01	Reference	Reference	2.54 (0.88, 7.31) P=0.08

\* Unadjusted (bivariable) and adjusted (multivariable)

#Adjusted for age, sex, race, index of co-existent disease, and body mass index

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**Table 4. Associations of Markers of Mineral Metabolism and Inflammation with Arteriovenous Fistula and Graft Intervention\***

	AVG		AVF	
	Unadjusted	Adjusted (age, race, sex, ICED, BMI)	Unadjusted	Adjusted (age, race, sex, ICED, BMI)
Log Calcium	1.02 (0.77, 1.36)	1.09 (0.79, 1.49)	0.90 (0.63, 1.28)	0.89 (0.60, 1.32)
Log Phosphorus	0.87 (0.68, 1.12)	0.88 (0.66, 1.17)	1.03 (0.64, 1.66)	1.12 (0.66, 1.89)
Log iPTH (81 AVF; 85 AVG)	0.98 (0.67, 1.44)	1.01 (0.67, 1.53)	<b>1.71</b> <b>(1.10, 2.67)</b> <b>P=0.02</b>	<b>1.67</b> <b>(1.00, 2.78)</b> <b>P=0.05</b>
Log CRP	0.97 (0.71, 1.33)	0.97 (0.69, 1.35)	1.21 (0.73, 1.98)	1.22 (0.67, 2.22)
Log IL-6	0.98 (0.70, 1.37)	0.95 (0.63, 1.42)	1.19 (0.86, 1.65)	1.20 (0.86, 1.68)

\* Unadjusted (bivariable) and adjusted (multivariable)

Per 1 SD higher

iPTH: intact parathyroid hormone; CRP: C-reactive protein; IL-6: interleukin-6.



**Table 5. Associations of Markers of Mineral Metabolism and Inflammation with Arteriovenous Fistula Intervention**

		<b>Adjusted# Relative Hazard (N=103)</b>	<b>Adjusted* Relative Hazard (N=81)</b>
25(OH)D	Tertile 1 (<11 ng/mL)	<b>3.28</b> <b>(1.31, 8.20)</b> <b>P=0.01</b>	<b>5.07</b> <b>(1.51, 17.0)</b> <b>P=0.009</b>
	Tertiles 2-3 (≥11 ng/mL)	Reference	Reference
FGF-23	Tertiles 1-2 (<3,750 RU/mL)	Reference	Reference
	Tertile 3 (≥3,750 RU/mL)	<b>2.56</b> <b>(1.06, 6.18)</b> <b>P=0.04</b>	<b>3.27</b> <b>(1.14, 9.40)</b> <b>P=0.03</b>
Log iPTH	Per SD	*	<b>1.64</b> <b>(1.02, 2.62)</b> <b>P=0.04</b>

#Adjusted for age, sex, race, body mass index, index of coexistent disease, FGF-23, 25(OH)D.

\*Adjusted multivariable for PTH in addition to the above.

**Table 6. Incidence of Arteriovenous Graft Intervention, by 25(OH)D and FGF-23 category\***

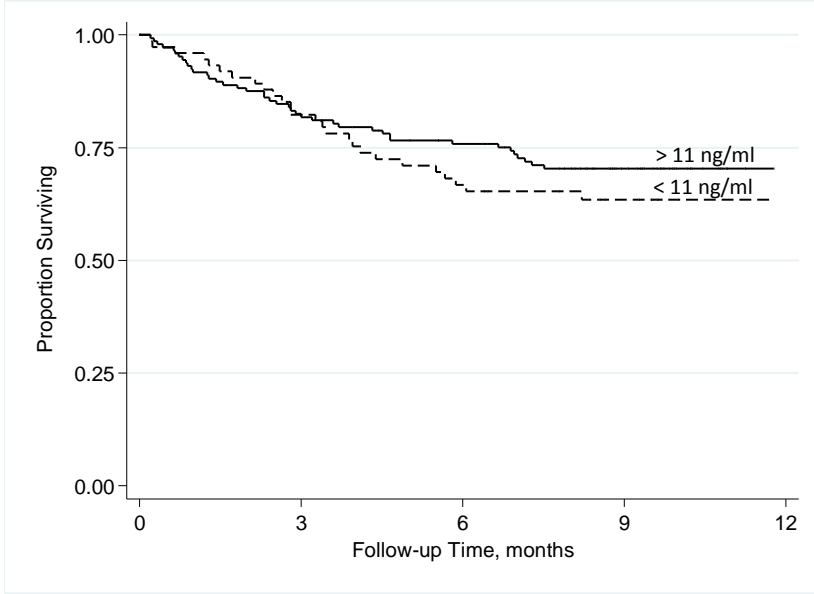
	25(OH)D		FGF-23	
	Tertile 1 ( $<11.0$ ng/mL)	Tertile 2-3 ( $\geq 11$ ng/mL)	Tertile 1-2 ( $<9,750$ RU/mL)	Tertile 3 ( $\geq 3,750$ RU/mL)
Events / N	15/44	28/72	30/82	13/34
Incidence Rate (per 100 person-months)	4.36	5.83	4.89	6.16
Unadjusted Relative Hazard	0.77 (0.41, 1.44)	Reference	Reference	1.14 (0.59, 2.18)

Adjusted# Relative Hazard	0.74 (0.39, 1.42)	Reference	Reference	1.16 (0.59, 2.25)
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\* Unadjusted (bivariable) and adjusted (multivariable)

#Adjusted for age, sex, race, index of co-existent disease, and body mass index

**Figure 1. Kapan-Meier survival curve for arteriovenous fistula, by tertiles of 25(OH)D**



**Figure 2. Adjusted incidence rate ratio for arteriovenous fistula, by 25(OH)D. Adjusted for age, sex, race, body mass index and index of coexistent disease**

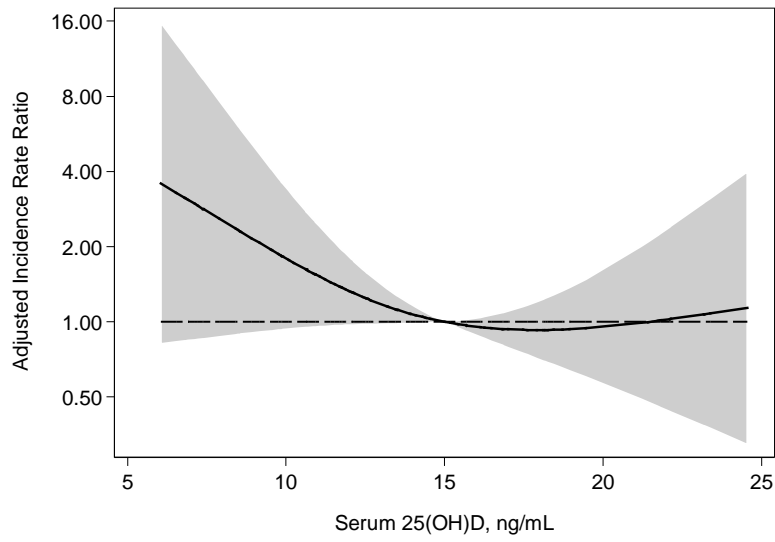
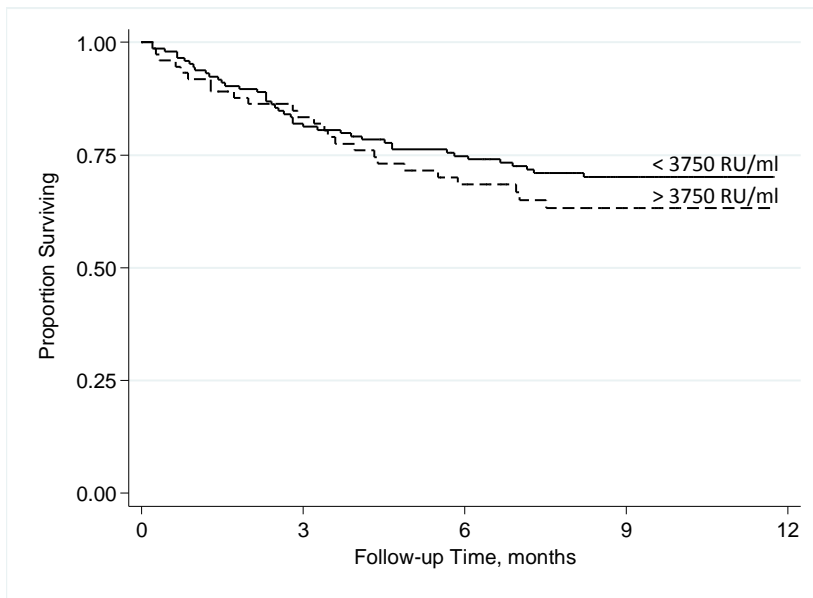
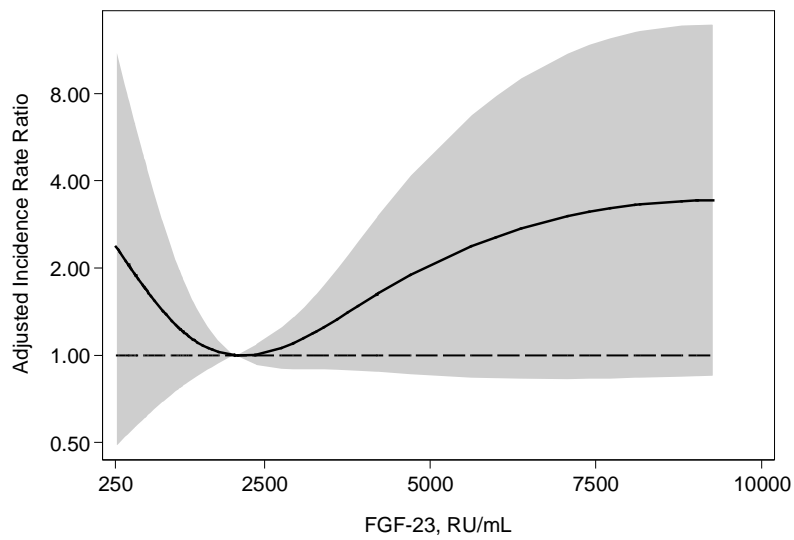


Figure 3. Kapan-Meier survival curve for arteriovenous fistula, by tertiles of FGF-23

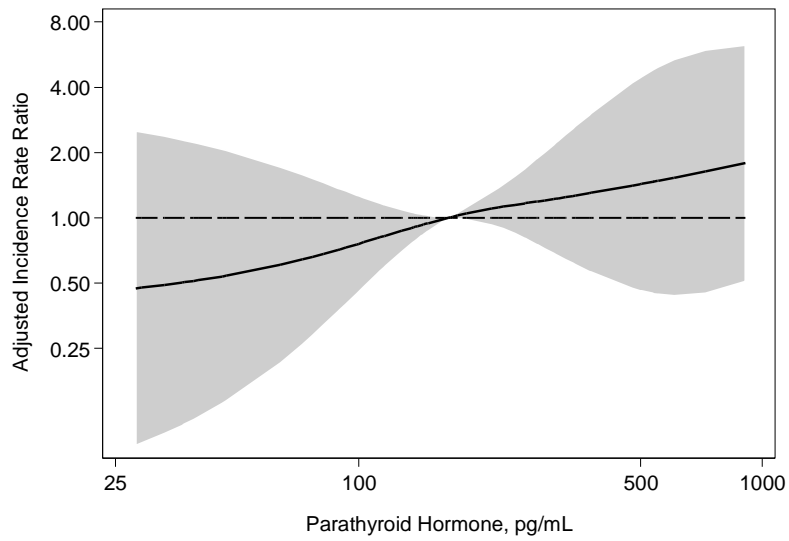


**Figure 4. Adjusted incidence rate ratio for arteriovenous fistula, by FGF-23. Adjusted for age, sex, race, body mass index and index of coexistent disease**



**Figure 5. Adjusted incidence rate ratio for arteriovenous fistula, by PTH. Adjusted for 25(OH)D and FGF-23**





**Table 1. Baseline characteristics, by 25(OH)D and FGF-23 category\***

	25(OH)D			FGF-23		
	Tertile 1 (<11 ng/mL)	Tertile 2-3 (≥11 ng/mL)	P	Tertile 1-2 (<3,750 RU/mL)	Tertile 3 (≥3,750 RU/mL)	P
N	74	145	-	145	74	-
Age, years	59.6 (11.5)	58.2 (15.9)	0.48	60.2 (14.4)	55.7 (14.4)	0.03
Female, %	36.5	59.2	0.002	50.3	54.1	0.60
Black, %	35.1	30.3	0.47	35.2	25.7	0.16
ICED	2.0 (0.8)	1.9 (0.8)	0.38	1.9 (0.8)	2.0 (0.8)	0.75
Body Mass Index, kg/m <sup>2</sup>	30.1 (7.3)	26.4 (5.8)	<0.00 1	27.4 (6.4)	28.2 (6.9)	0.43
25(OH)D, ng/mL	8.8 (1.5)	17.3 (5.4)	-	14.2 (5.5)	15.1 (6.9)	0.29
FGF-23, RU/mL	3581 (4398)	4713 (5099)	0.11	1,392 (923)	10,088 (4365)	-
Calcium, mg/dl	9.0 (0.6)	9.3 (0.7)	0.006	9.1 (0.6)	9.3 (0.7)	0.08
Phosphorus, mg/dl	5.2 (1.2)	5.4 (1.3)	0.18	5.0 (1.1)	6.0 (1.2)	<0.001
iPTH, pg/ml	222 (172)	290 (415)	0.22	228 (323)	333 (365)	0.06
CRP, mg/dl	1.0 (1.5)	0.7 (1.0)	0.03	0.7 (1.1)	0.9 (1.3)	0.43
IL-6, mg/dl	8.9 (15.9)	6.3 (9.9)	0.13	7.0 (12.1)	7.5 (12.7)	0.77
Arteriovenous Fistula, %	40.1	50.3	0.17	43.4	54.1	0.14

\* baseline characteristics (unadjusted = bivariable)

ICED: Index of Co-Existent Diseases; iPTH: Intact parathyroid hormone (n=166)

**Table 2. Correlations between markers of mineral metabolism and inflammation\***

	25(OH)D	FGF-23	Calcium	Phosphorus	iPTH (n=166)	CRP
FGF-23	0.11	-	-	-	-	-
Calcium	<b>0.28</b> ( <b>&lt;0.001</b> )	<b>0.18</b> ( <b>0.007</b> )	-	-	-	-
Phosphorus	0.07	<b>0.43</b> ( <b>&lt;0.001</b> )	0.02	-	-	-
iPTH (n=166)	-0.07	0.12	<b>-0.31</b> ( <b>&lt;0.001</b> )	0.16	-	-
CRP	-0.08	0.07	-0.07	-0.01	-0.02	-
IL-6	-0.07	0.11	<b>-0.16</b> ( <b>0.02</b> )	0.01	0.10	<b>0.55</b> ( <b>&lt;0.001</b> )

\*Correlations based on Unadjusted Log Values of each marker.

25(OH)D: 25-hydroxy vitamin D; FGF-23: Fibroblast growth factor-23; iPTH: intact parathyroid hormone; CRP: C-reactive protein; IL-6: interleukin-6.

**Table 3. Incidence of Arteriovenous Fistula Intervention, by 25(OH)D and FGF-23 category\***

	25(OH)D		FGF-23	
	Tertile 1 (<11.0 ng/mL)	Tertile 2-3 (≥11 ng/mL)	Tertile 1-2 (<9,750 RU/mL)	Tertile 3 (≥3,750 RU/mL)
Events / N	11/30	13/73	12/63	12/40
Incidence Rate (per 100 person-months)	5.34	2.05	2.19	4.14
Unadjusted Relative Hazard	2.50 (1.12, 5.60)	Reference	Reference	1.76 (0.79, 3.93)
Adjusted# Relative Hazard	2.74 (1.13, 6.64)	Reference	Reference	2.15 (0.90, 5.15)
Unadjusted + Log Phosphorus	2.90 (1.22, 6.92) P=0.02	Reference	Reference	2.22 (0.81, 6.09) P=0.12
Adjusted# + Log Phosphorus	3.38 (1.30, 8.80) P=0.01	Reference	Reference	2.54 (0.88, 7.31) P=0.08

\* Unadjusted (bivariable) and adjusted (multivariable)

#Adjusted for age, sex, race, index of co-existent disease, and body mass index

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**Table 4. Associations of Markers of Mineral Metabolism and Inflammation with Arteriovenous Fistula and Graft Intervention\***

	AVG		AVF	
	Unadjusted	Adjusted (age, race, sex, ICED, BMI)	Unadjusted	Adjusted (age, race, sex, ICED, BMI)
Log Calcium	1.02 (0.77, 1.36)	1.09 (0.79, 1.49)	0.90 (0.63, 1.28)	0.89 (0.60, 1.32)
Log Phosphorus	0.87 (0.68, 1.12)	0.88 (0.66, 1.17)	1.03 (0.64, 1.66)	1.12 (0.66, 1.89)
Log iPTH (81 AVF; 85 AVG)	0.98 (0.67, 1.44)	1.01 (0.67, 1.53)	<b>1.71</b> <b>(1.10, 2.67)</b> <b>P=0.02</b>	<b>1.67</b> <b>(1.00, 2.78)</b> <b>P=0.05</b>
Log CRP	0.97 (0.71, 1.33)	0.97 (0.69, 1.35)	1.21 (0.73, 1.98)	1.22 (0.67, 2.22)
Log IL-6	0.98 (0.70, 1.37)	0.95 (0.63, 1.42)	1.19 (0.86, 1.65)	1.20 (0.86, 1.68)

\* Unadjusted (bivariable) and adjusted (multivariable)

Per 1 SD higher

iPTH: intact parathyroid hormone; CRP: C-reactive protein; IL-6: interleukin-6.

**Table 5. Associations of Markers of Mineral Metabolism and Inflammation with Arteriovenous Fistula Intervention**

		<b>Adjusted# Relative Hazard (N=103)</b>	<b>Adjusted* Relative Hazard (N=81)</b>
25(OH)D	Tertile 1 (<11 ng/mL)	<b>3.28</b> <b>(1.31, 8.20)</b> <b>P=0.01</b>	<b>5.07</b> <b>(1.51, 17.0)</b> <b>P=0.009</b>
	Tertiles 2-3 (≥11 ng/mL)	Reference	Reference
FGF-23	Tertiles 1-2 (<3,750 RU/mL)	Reference	Reference
	Tertile 3 (≥3,750 RU/mL )	<b>2.56</b> <b>(1.06, 6.18)</b> <b>P=0.04</b>	<b>3.27</b> <b>(1.14, 9.40)</b> <b>P=0.03</b>
Log iPTH	Per SD	*	<b>1.64</b> <b>(1.02, 2.62)</b> <b>P=0.04</b>

#Adjusted for age, sex, race, body mass index, index of coexistent disease, FGF-23, 25(OH)D.

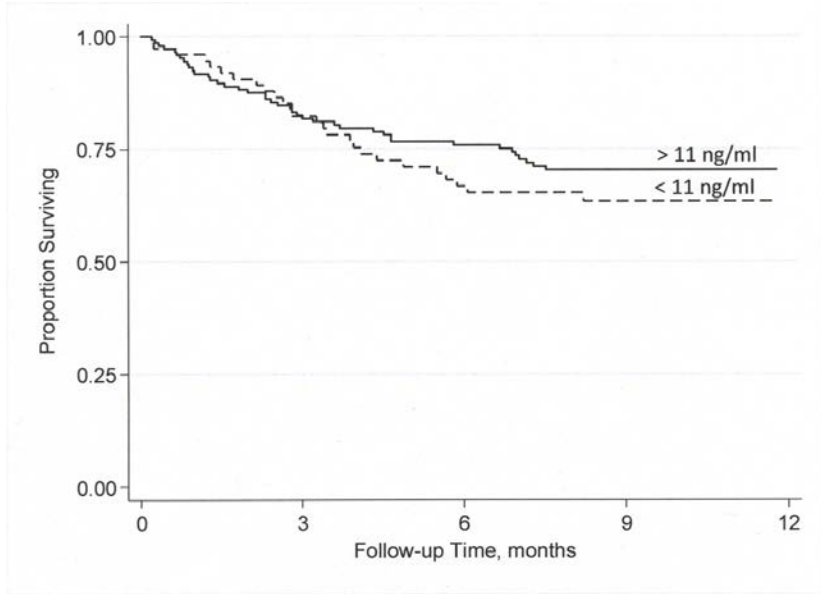
\*Adjusted multivariable for PTH in addition to the above.

**Table 6. Incidence of Arteriovenous Graft Intervention, by 25(OH)D and FGF-23 category\***

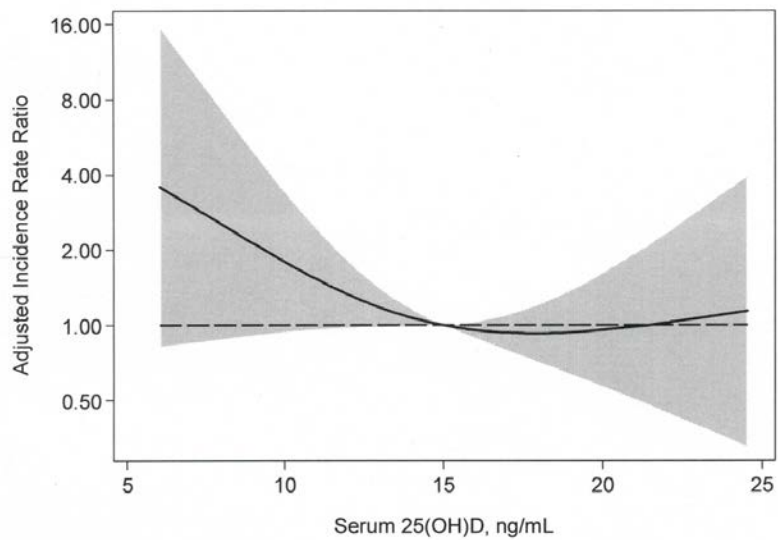
	25(OH)D		FGF-23	
	Tertile 1 (<11.0 ng/mL)	Tertile 2-3 (≥11 ng/mL)	Tertile 1-2 (<9,750 RU/mL)	Tertile 3 (≥3,750 RU/mL)
Events / N	15/44	28/72	30/82	13/34
Incidence Rate (per 100 person-months)	4.36	5.83	4.89	6.16
Unadjusted Relative Hazard	0.77 (0.41, 1.44)	Reference	Reference	1.14 (0.59, 2.18)
Adjusted# Relative Hazard	0.74 (0.39, 1.42)	Reference	Reference	1.16 (0.59, 2.25)

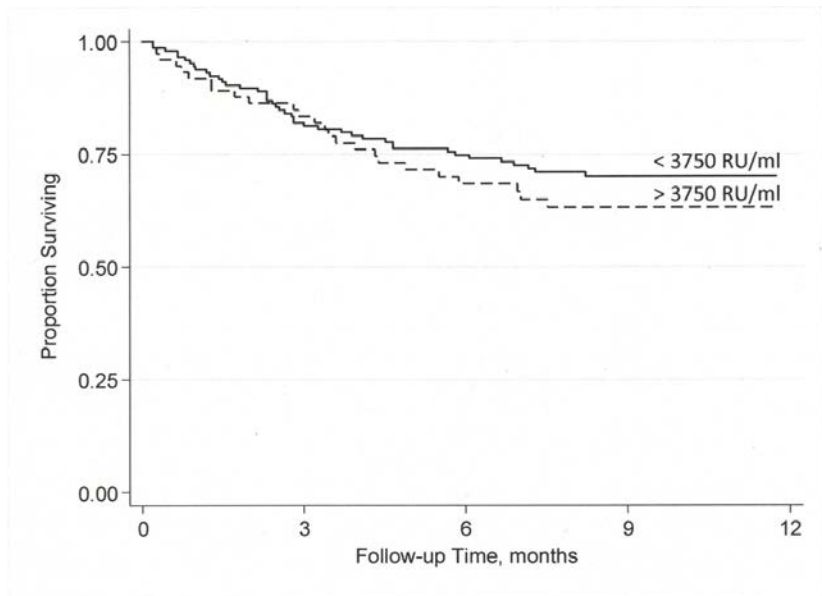
\* Unadjusted (bivariable) and adjusted (multivariable)

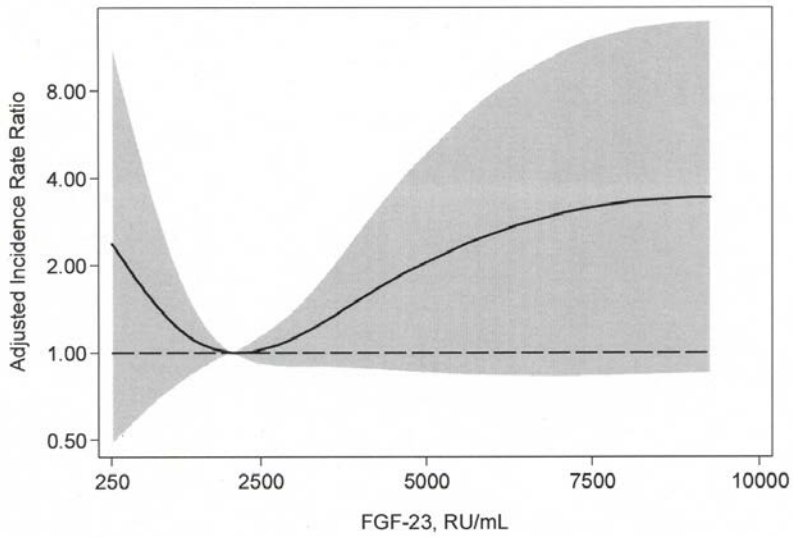
#Adjusted for age, sex, race, index of co-existent disease, and body mass index

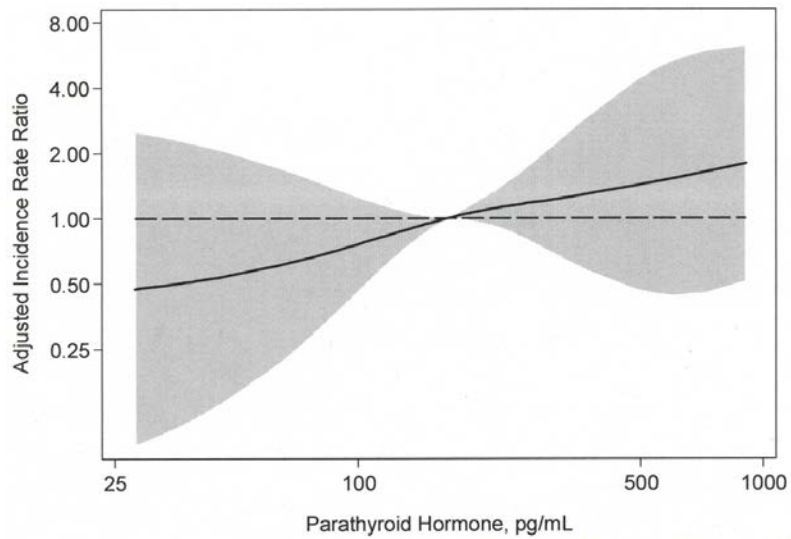


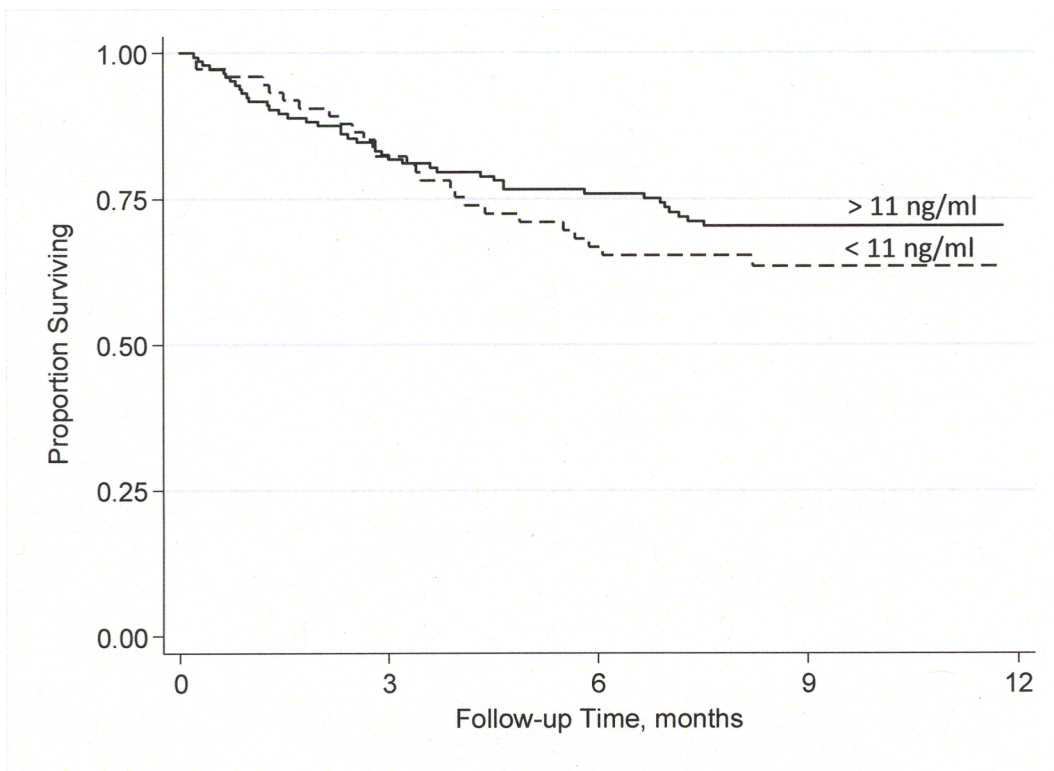




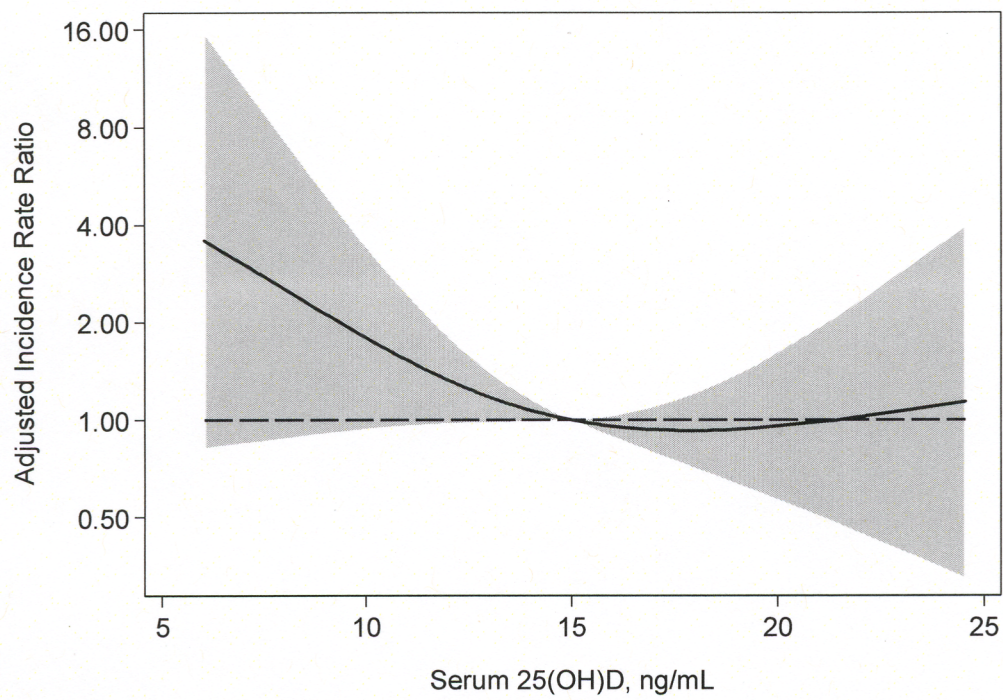




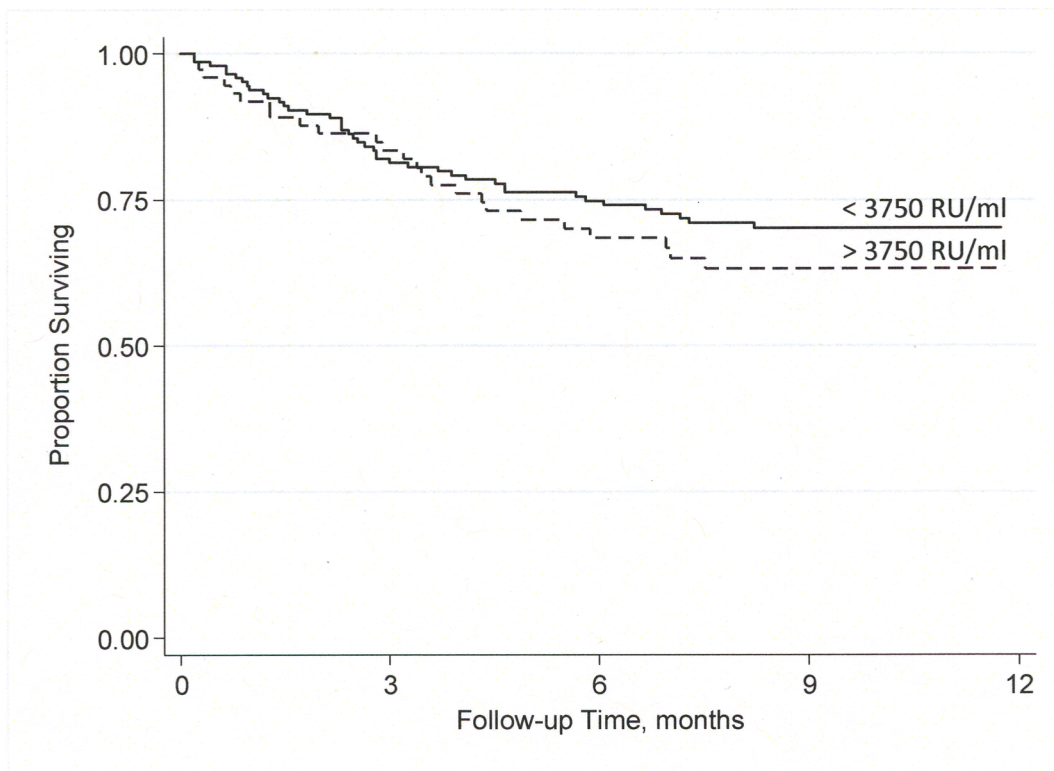




HDI\_12798\_Figure 1 .tif

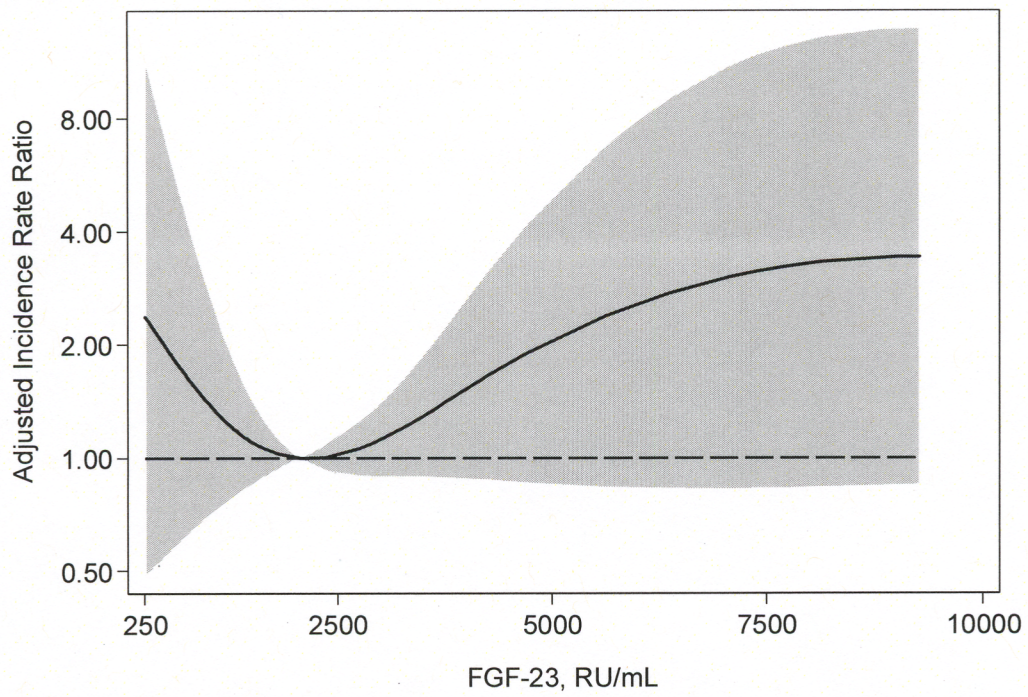


HDI\_12798\_Figure 2 .tif



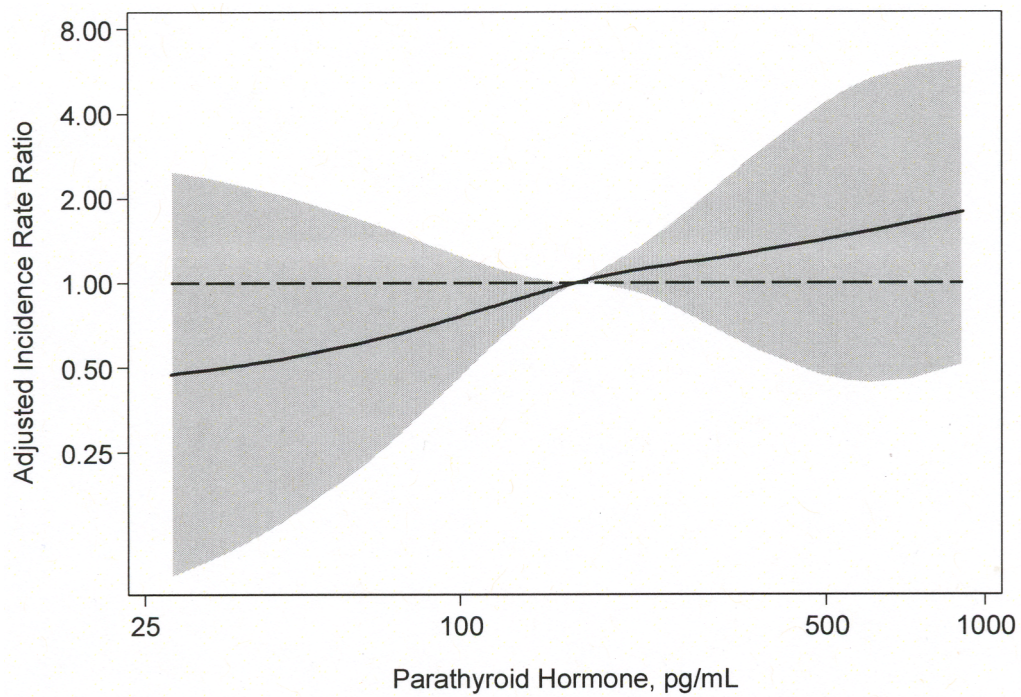
HDI\_12798\_Figure 3.tif





HDI\_12798\_Figure 4.tif





HDI\_12798\_Figure 5.tif

**Table 1. Baseline characteristics, by 25(OH)D and FGF-23 category\***

	25(OH)D			FGF-23		P
	Tertile 1 ( $<11$ ng/mL)	Tertile 2-3 ( $\geq 11$ ng/mL)	P	Tertile 1-2 ( $<3,750$ RU/mL)	Tertile 3 ( $\geq 3,750$ RU/mL)	
N	74	145	-	145	74	-
Age, years	59.6 (11.5)	58.2 (15.9)	0.48	60.2 (14.4)	55.7 (14.4)	0.03
Female, %	36.5	59.2	0.002	50.3	54.1	0.60
Black, %	35.1	30.3	0.47	35.2	25.7	0.16
ICED	2.0 (0.8)	1.9 (0.8)	0.38	1.9 (0.8)	2.0 (0.8)	0.75
Body Mass Index, kg/m <sup>2</sup>	30.1 (7.3)	26.4 (5.8)	$<0.001$	27.4 (6.4)	28.2 (6.9)	0.43
25(OH)D, ng/mL	8.8 (1.5)	17.3 (5.4)	-	14.2 (5.5)	15.1 (6.9)	0.29
FGF-23, RU/mL	3581 (4398)	4713 (5099)	0.11	1,392 (923)	10,088 (4365)	-
Calcium, mg/dl	9.0 (0.6)	9.3 (0.7)	0.006	9.1 (0.6)	9.3 (0.7)	0.08
Phosphorus, mg/dl	5.2 (1.2)	5.4 (1.3)	0.18	5.0 (1.1)	6.0 (1.2)	$<0.001$
iPTH, pg/ml	222 (172)	290 (415)	0.22	228 (323)	333 (365)	0.06
CRP, mg/dl	1.0 (1.5)	0.7 (1.0)	0.03	0.7 (1.1)	0.9 (1.3)	0.43
IL-6, mg/dl	8.9 (15.9)	6.3 (9.9)	0.13	7.0 (12.1)	7.5 (12.7)	0.77
Arteriovenous Fistula, %	40.1	50.3	0.17	43.4	54.1	0.14

\* baseline characteristics (unadjusted = bivariable)

ICED: Index of Co-Existent Diseases; iPTH: Intact parathyroid hormone (n=166)

**Table 2. Correlations between markers of mineral metabolism and inflammation\***

	25(OH)D	FGF-23	Calcium	Phosphorus	iPTH (n=166)	CRP
FGF-23	0.11	-	-	-	-	-
Calcium	<b>0.28</b> ( <b>&lt;0.001</b> )	<b>0.18</b> ( <b>0.007</b> )	-	-	-	-
Phosphorus	0.07	<b>0.43</b> ( <b>&lt;0.001</b> )	0.02	-	-	-
iPTH (n=166)	-0.07	0.12	<b>-0.31</b> ( <b>&lt;0.001</b> )	0.16	-	-
CRP	-0.08	0.07	-0.07	-0.01	-0.02	-
IL-6	-0.07	0.11	<b>-0.16</b> ( <b>0.02</b> )	0.01	0.10	<b>0.55</b> ( <b>&lt;0.001</b> )

\*Correlations based on Unadjusted Log Values of each marker.

25(OH)D: 25-hydroxy vitamin D; FGF-23: Fibroblast growth factor-23; iPTH: intact parathyroid hormone; CRP: C-reactive protein; IL-6: interleukin-6.

**Table 3. Incidence of Arteriovenous Fistula Intervention, by 25(OH)D and FGF-23 category\***

	25(OH)D		FGF-23	
	Tertile 1 ( $<11.0$ ng/mL)	Tertile 2-3 ( $\geq 11$ ng/mL)	Tertile 1-2 ( $<9,750$ RU/mL)	Tertile 3 ( $\geq 3,750$ RU/mL)
Events / N	11/30	13/73	12/63	12/40
Incidence Rate (per 100 person-months)	5.34	2.05	2.19	4.14
Unadjusted Relative Hazard	2.50 (1.12, 5.60)	Reference	Reference	1.76 (0.79, 3.93)
Adjusted# Relative Hazard	2.74 (1.13, 6.64)	Reference	Reference	2.15 (0.90, 5.15)
Unadjusted + Log Phosphorus	2.90 (1.22, 6.92) P=0.02	Reference	Reference	2.22 (0.81, 6.09) P=0.12
Adjusted# + Log Phosphorus	3.38 (1.30, 8.80) P=0.01	Reference	Reference	2.54 (0.88, 7.31) P=0.08

\* Unadjusted (bivariable) and adjusted (multivariable)

#Adjusted for age, sex, race, index of co-existent disease, and body mass index

**Table 4. Associations of Markers of Mineral Metabolism and Inflammation with Arteriovenous Fistula and Graft Intervention\***

	AVG		AVF	
	Unadjusted	Adjusted (age, race, sex, ICED, BMI)	Unadjusted	Adjusted (age, race, sex, ICED, BMI)
Log Calcium	1.02 (0.77, 1.36)	1.09 (0.79, 1.49)	0.90 (0.63, 1.28)	0.89 (0.60, 1.32)
Log Phosphorus	0.87 (0.68, 1.12)	0.88 (0.66, 1.17)	1.03 (0.64, 1.66)	1.12 (0.66, 1.89)
Log iPTH (81 AVF; 85 AVG)	0.98 (0.67, 1.44)	1.01 (0.67, 1.53)	<b>1.71</b> <b>(1.10, 2.67)</b> <b>P=0.02</b>	<b>1.67</b> <b>(1.00, 2.78)</b> <b>P=0.05</b>
Log CRP	0.97 (0.71, 1.33)	0.97 (0.69, 1.35)	1.21 (0.73, 1.98)	1.22 (0.67, 2.22)
Log IL-6	0.98 (0.70, 1.37)	0.95 (0.63, 1.42)	1.19 (0.86, 1.65)	1.20 (0.86, 1.68)

\* Unadjusted (bivariable) and adjusted (multivariable)

Per 1 SD higher

iPTH: intact parathyroid hormone; CRP: C-reactive protein; IL-6: interleukin-6.

**Table 5. Associations of Markers of Mineral Metabolism and Inflammation with Arteriovenous Fistula Intervention**

		<b>Adjusted# Relative Hazard (N=103)</b>	<b>Adjusted* Relative Hazard (N=81)</b>
25(OH)D	Tertile 1 (<11 ng/mL)	<b>3.28</b> <b>(1.31, 8.20)</b> <b>P=0.01</b>	<b>5.07</b> <b>(1.51, 17.0)</b> <b>P=0.009</b>
	Tertiles 2-3 (≥11 ng/mL)	Reference	Reference
FGF-23	Tertiles 1-2 (<3,750 RU/mL)	Reference	Reference
	Tertile 3 (≥3,750 RU/mL)	<b>2.56</b> <b>(1.06, 6.18)</b> <b>P=0.04</b>	<b>3.27</b> <b>(1.14, 9.40)</b> <b>P=0.03</b>
Log iPTH	Per SD	*	<b>1.64</b> <b>(1.02, 2.62)</b> <b>P=0.04</b>

#Adjusted for age, sex, race, body mass index, index of coexistent disease, FGF-23, 25(OH)D.

\*Adjusted multivariable for PTH in addition to the above.

**Table 6. Incidence of Arteriovenous Graft Intervention, by 25(OH)D and FGF-23 category\***

	25(OH)D		FGF-23	
	Tertile 1 (<11.0 ng/mL)	Tertile 2-3 (≥11 ng/mL)	Tertile 1-2 (<9,750 RU/mL)	Tertile 3 (≥3,750 RU/mL)
Events / N	15/44	28/72	30/82	13/34
Incidence Rate (per 100 person-months)	4.36	5.83	4.89	6.16
Unadjusted Relative Hazard	0.77 (0.41, 1.44)	Reference	Reference	1.14 (0.59, 2.18)
Adjusted# Relative Hazard	0.74 (0.39, 1.42)	Reference	Reference	1.16 (0.59, 2.25)

\* Unadjusted (bivariable) and adjusted (multivariable)

#Adjusted for age, sex, race, index of co-existent disease, and body mass index