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Relationship of 1,25 dihydroxy Vitamin D Levels to Clinical Outcomes in Critically Ill Patients with Acute Kidney Injury

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Abstract

Background: Calcitriol [1,25$(OH)_2$D] plays a central role in endocrine regulation of bone and mineral metabolism. Low 1,25$(OH)_2$D levels in chronic kidney disease (CKD) are associated with increased cardiovascular morbidity and mortality. However, the role of 1,25$(OH)_2$D in acute kidney injury (AKI) is unclear, with very limited data. This pilot study examined the relationship between 1,25$(OH)_2$D levels in critically ill patients with AKI and clinical outcomes.

Methods: Plasma 1,25$(OH)_2$D, intact parathyroid hormone (iPTH), 25-OH Vitamin D (VitD), calcium and phosphorus were measured in 34 patients with AKI without pre-existing chronic kidney disease and 12 healthy controls.

Results: The mean 1,25$(OH)_2$D levels were significantly lower in patients with AKI compared to controls, (42 ± 5.6 pg/mL vs. 76.1 ± 5.3 pg/mL, P<0.0001). The mortality in patients with AKI was 30%. 1,25$(OH)_2$D levels were higher in non-survivors than survivors (62 ± 41.4 pg/mL vs. 33.7 ± 24.2 pg/mL respectively, P=0.046) and serum phosphorus was also higher in non-survivors (6.2 ± 2.1 mg/dL vs. 4.6 ± 1.6 mg/dL, P=0.019). However, on multivariate regression analysis, accounting for age and APACHE II score, higher levels of 1,25$(OH)_2$D was not associated with mortality in critically ill patients with AKI.

Conclusion: Mineral metabolism is dysregulated within days of acute renal injury in critically ill patients. On univariate analysis, high levels of calcitriol were associated with adverse clinical outcome in AKI. This association was not apparent after adjusting for age and APACHE II. Large controlled studies are needed to confirm these results, and determine if higher 1,25$(OH)_2$D mediates worse outcomes in AKI.

Keywords: Calcitriol; Intact parathyroid hormone; Acute tubular necrosis

Introduction

Acute kidney injury (AKI) in critically ill patients is associated with poor outcome. Despite major advances in renal replacement therapies over the past five decades, mortality in the critically ill population with AKI remains about 50% [1]. Observational studies suggest that the increased mortality in patients with AKI cannot be explained by other comorbidities alone, and that renal injury itself is independently associated with the negative outcome [2]. While renal replacement therapy (RRT) rectifies acid-base, electrolyte and volume abnormalities, it does not restore the endocrine or immunologic functions of a normal kidney. Increasing dose of RRT has not shown to improve survival in AKI [3,4].

Endocrine function of the kidney includes the conversion of 25-OH Vitamin D to 1,25-OH Vitamin D [1,25$(OH)_2$D] [5,6]. In chronic kidney disease (CKD), 1,25$(OH)_2$D levels start to decline in stage 2, and continue to decrease as glomerular filtration rate falls [7]. The overwhelming majority of CKD patients initiating hemodialysis have low 1,25$(OH)_2$D levels, and the lowest levels correlate with significantly higher mortality during the first 90 days of dialysis [8]. In the general population, low 1,25$(OH)_2$D levels have been associated with left ventricular hypertrophy, heart failure, and higher mortality [9-11].

There are limited data on 1,25$(OH)_2$D levels in patients with AKI, and the relationship of 1,25$(OH)_2$D to clinical outcomes in patients with AKI has not been elucidated. We conducted a prospective cohort study to evaluate 1,25$(OH)_2$D levels and other markers of mineral metabolism in critically ill patients with AKI and their relationship to mortality and need for dialysis. We hypothesized that 1,25$(OH)_2$D would be low in AKI, and that lower levels would directly correlate with higher mortality, as has been observed in the CKD and chronic dialysis populations.

Methods

The protocol was approved by the human research protection office at Washington University in St. Louis and informed written consent was obtained from all participants or their legally authorized representatives with the help of Kidney Translational Research Core (KTRC). Over a 6-month period, we identified 34 critically ill patients at Barnes-Jewish Hospital who had a clinical diagnosis of Stage 2 or 3 AKI, according to the Acute Kidney Injury Network (AKIN) diagnosis and staging classification [12]. Stage 2 AKI is defined as increase in serum creatinine (SCr) greater than 200% to 300% from baseline and Stage 3 is defined as increase in SCr to more than 300% from baseline, or more than or equal to 4.0 mg/dL with an acute increase of at least 0.5 mg/dL or on RRT. All patients had a nephrology consultation prior to enrollment in the study and a clinical diagnosis of acute tubular necrosis (ATN) was documented in the chart by a nephrology attending physician. Patients with a renal diagnosis other than ATN and those with CKD with estimated baseline GFR of <60 ml/min/1.73m^2 based on the modification of diet in renal disease (MDRD) equation were excluded [13]. Patients who were on vitamin D supplementation were excluded from the study. The serum creatinine immediately prior to onset of AKI (lowest SCr in past 30 days prior to the hospitalization if

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	AKI (n = 34)	Healthy controls (n = 12)	P Value
Age (years)	51.9±17.8	45.3 ±16.9	NS
Female	56%	58%	NS
Caucasian	91%	92%	NS
25-OH VitD (ng/mL)	13.0 ± 6.3	29.2 ± 9.4	<0.0001
(Reference range 30-100ng/mL)			
iPTH (pg/mL)	134.4 ± 24.7	12.3 ± 3.7	<0.0001
(Reference range 14-72 pg/mL)			
1,25(OH)$_2$D (pg/mL)	42 ± 5.6	76.1 ± 5.3	<0.0001
(Reference range 18-78 pg/mL)			
AKI - Acute Kidney Injury			

Table 1: Clinical Characteristics and Laboratory Data of Patients with AKI and Healthy Controls.

	Survivors (N = 24)	Non-survivors (N = 10)	P Value
Age (years)	52 ± 14	52 ± 19	NS
Female (%)	13 (54)	6 (60)	NS
Caucasian (%)	23 (96)	8 (80)	NS
Diabetes Mellitus (%)	5 (21)	1 (10)	NS
Hypertension (%)	12 (50)	4 (40)	NS
Cardiac disease (%)	7 (29)	4 (40)	NS
Malignancy (%)	4 (17)	3 (30)	NS
Sepsis (%)	9 (38)	5 (50)	NS
Apache II	22.3 ± 10.5	31.8 ± 5.3	0.001
Baseline SCr (mean, mg/dL)	1.0 ± 0.37	0.86 ± 0.17	NS
Days from Diagnosis of AKI to Sample Collection (mean)	3.0 ± 1.5	4.8 ± 3.3	NS
Need for RRT	58%	40%	NS
Etiology of AKI (%)			
Sepsis	8 (33.3)	5 (50)	
Ischemia	5 (20.8)	3 (30)	
Multifactorial	7 (29.2)	2 (20)	
Nephrotoxin	2 (8.3)	0	
Rhabdomyolysis	2 (8.3)	0	
AKI – Acute Kidney Injury			

Table 2: Baseline Characteristics of Patients with AKI.

AKI was present on admission or lowest SCr in hospital prior to rise of SCr for hospital acquired AKI) was considered as the baseline serum creatinine.

Twelve healthy volunteers who were recruited from the ambulatory setting were used as controls. Plasma samples obtained from AKI patients and healthy volunteers were derived from peripheral blood and stored at -80°C by the KTRC. For the critically ill patients, samples were collected within 10 days of the diagnosis of AKI. Calcium, phosphorus and creatinine were obtained as part of routine care of the critically ill patients and were not available for the healthy controls. 25-hydroxy vitamin D and 1,25(OH)$_2$D levels were quantified using the radioimmunoassay kit from Immunodiagnostic Systems (Scottsdale, AZ). PTH was measured using the ELISA kit for human bioactive PTH 1-84 from Immutopics International (San Clemente, CA).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp Armonk, NY). We compared baseline characteristics of healthy controls to the patients with AKI, and the variables for survivors versus non-survivors in the critically ill AKI population. Categorical variables were expressed as proportions and compared using the Chi-squared test. Continuous variables are expressed as mean ± standard deviation and were compared using the Mann-Whitney rank-sum test or *t* test where appropriate. Linear regression analysis was used to evaluate whether 1,25(OH)$_2$D was a predictor of mortality, controlling for age and APACHE II score.

Results

The mean age of the AKI patients was 51.9 years, with 56% female and 91% Caucasian. The mean age of the healthy controls was 45.3 years (Table 1). The patients with AKI had significantly lower mean 25-OH vitamin D and 1,25(OH)$_2$D levels than the healthy controls (P<0.01 for both comparisons), while plasma iPTH was significantly higher than the healthy controls (P<0.05). Even though 1,25(OH)$_2$D levels in AKI patients were lower than the controls, they remained within the laboratory reference range. Eighteen patients (53%) required renal replacement therapy. The in-hospital mortality among the AKI patients was 10 of 34 (30%), and 4 of these 10 received RRT prior to death. The cause of death was sepsis (5), cardiac event (3) and multi-organ failure (2) (Table 2).

Table 2 compares the clinical characteristics between the non-survivors and survivors among the AKI patients. The average time from diagnosis of AKI to sample collection was not different between groups (4.8 days in non-survivors versus 3.3, P=0.13). Baseline serum creatinine (prior to onset of AKI) values were available in 23 patients with AKI and were not statistically different between the groups. The APACHE II was higher in non-survivors (31.8 vs. 22.3, p=0.001). The distribution of 1,25(OH)$_2$D levels in survivors and non-survivors is shown in Figure 1. Only plasma 1,25(OH)$_2$D (P=0.046) and phosphorus (P = 0.019) levels were significantly higher in the non-survivors versus the survivors (Table 3). The calcium and 25-OH vitamin D levels did not differ between the groups.

A total of 24 of 34 (70%) reached a combined endpoint of death and/or need for RRT. The mean 1,25(OH)$_2$D level was significantly higher in this group (49.4 ± 34.9 vs. 24.1 ± 15.0, P=0.006) compared to survivors and those not requiring RRT. Univariate logistic regression demonstrated that higher1,25(OH)$_2$D levels were associated with a higher risk of death in AKI patients (P=0.04, OR 1.029). Higher serum phosphorus levels (P = 0.02, OR 1.629) and APACHE II scores

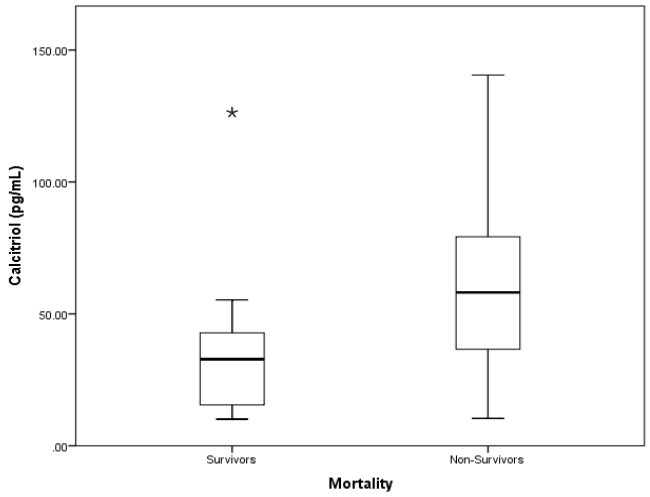

Figure 1: 1,25(OH)$_2$D levels in patients with AKI: Non-survivors had Significantly Higher 1,25(OH)$_2$D Levels Compared to Survivors (P = 0.046). The Box extends from 25th to 75th percentile and the Line in the Box Represents the Median. The Symbol * Represents the Outlier.

	Survivors (n = 24)	Non-survivors (n = 10)	P Value
Peak SCr (mg/dL)	4.9 ± 2.8	3.7 ± 1.4	0.401
Calcium (mg/dL)	8.1 ± 0.8	8.2 ± 1.1	0.625
Phosphorus (mg/dL)	4.6 ± 1.6	6.2 ± 2.1	0.019
25OH VitD (ng/mL)	13.4 ± 6.6	12 ± 5.5	0.564
Intact PTH (pg/mL)	123.4 ± 133	160.8 ± 171.8	0.642
1,25(OH)$_2$D (pg/mL)	33.7 ± 24.2	62 ± 41.4	0.046
SCr – serum creatinine; AKI – acute kidney injury; RRT – renal replacement therapy;			

Table 3: Laboratory Data in Patients with AKI.

Predictor	Coefficient	95% CI	P Value
1,25(OH)$_2$D	0.29	.000 – .009	0.069
APACHE II	0.51	.006 – .040	0.009
Sepsis	-0.32	-0.17 – .001	0.078

Table 4: Multivariable Linear Regression Analysis.

(P=0.027, OR 1.142) were also associated with increased risk for mortality. On multivariate regression analysis, adjusting for need for age and APACHE II, higher plasma 1,25(OH)$_2$D was not associated with increased risk for death (P=0.069) (Table 4).

Discussion

The beneficial role of 1,25(OH)$_2$D in CKD has been extensively characterized in numerous studies [14]. In addition to its effects on bone and mineral metabolism, low 1,25(OH)$_2$D levels are associated with increased risk of cardiovascular events and death in both CKD and dialysis patients [11,15]. Conversely, administration of calcitriol or other forms of active vitamin D to such patients are associated with improved outcomes [16-18].

Pre-clinical studies have demonstrated that 1,25(OH)$_2$D levels in dogs with AKI are significantly lower than healthy animals [19]. Ischemic and toxic insults result in injury to the proximal tubules, the major site of 1,25(OH)$_2$D production in the kidney [20]. Fibroblast growth factor-23 (FGF-23) is known to down-regulate the renal 1α-hydroxylase which produces 1,25(OH)$_2$D, and levels of these hormones are inversely correlated. Recent studies have demonstrated that (FGF-23) levels are elevated in AKI and associated with increased risk for death and/or RRT [21,22]. However only 2 other studies have evaluated 1,25(OH)$_2$D and other markers of bone and mineral metabolism in the setting of AKI [21,23]. In a single center prospective study with 60 patients, Leaf et al showed that 1,25(OH)$_2$D levels were significantly decreased in patients with AKI compared to hospitalized patients without AKI [21]. We found that mean 1,25(OH)$_2$D levels in AKI patients were significantly lower than healthy controls when measured at a mean of 3.5 ± 2.3 days after onset of AKI, but remained within our laboratory reference range. In contrast, Leaf et al. reported a significantly lower mean 1,25(OH)$_2$D level, which was below the reference range at both day 1 and day 5 of AKI. The explanation for differences between these studies is not apparent, as both studies measured 1,25(OH)$_2$D levels at similar time points in AKI patients with a comparable risk of RRT and death.

The hormone, 1,25(OH)$_2$D, plays an integral role in immunomodulation, and has been proposed as a potential therapeutic agent in some autoimmune disorders [14,24]. In one small study, administration of vitamin D to chronic hemodialysis patients reduced inflammatory cytokines such as IL-8, IL-6 and TNFα [25]. Vitamin D analogs have also been shown to have anti-inflammatory effects in patients with CKD [26]. These and other observations have led to the hypothesis that 1,25(OH)$_2$D deficiency contributes to the burden of cardiovascular and total mortality observed in patients with CKD [11]. We therefore hypothesized that 1,25(OH)$_2$D levels would be decreased in AKI, and that lower levels would be associated with increased risk for death.

Contrary to our expectation, on univariate analysis, higher 1,25(OH)$_2$D levels correlated with an increased risk of death and death plus RRT in AKI patients. The increased risk of death was only 2.9%, but statistically significant. Leaf et al found higher FGF-23 levels in patients with AKI were associated with increased risk for mortality and/or need for RRT. While Leaf et al found the expected inverse relationship of FGF-23 levels to 1,25(OH)$_2$D in the AKI group, they did not find an association between 1,25(OH)$_2$D and the risk of death and/or AKI, and did not report any relationship of these factors to the risk of death alone [21]. Animal studies have noted that FGF-23 levels in AKI are independent of 1,25(OH)$_2$D levels and that might explain the discrepancy in the results [27]. A more recent study by Lai et al also did not find an association between 1,25(OH)$_2$D levels and 90-day all-cause mortality in hospital-acquired AKI [23].

Production of 1,25(OH)$_2$D is not solely limited to the kidney, though the kidneys are the dominant source of circulating 1,25(OH)$_2$D in health. Macrophages possess 1α-hydroxylase, and may cause marked extra-renal production of 1,25(OH)$_2$D in the setting of tuberculosis and some fungal infections, as well as sarcoidosis. Macrophage activation is also well documented in sepsis and this could potentially lead to extra-renal 1,25(OH)$_2$D production, and therefore associate higher 1,25(OH)$_2$D levels with higher mortality [28]. In our study, 1,25(OH)$_2$D levels were higher in patients with sepsis (51.7 ± 43.4 vs. 35.2 ± 20.3 pg/mL), but this did not reach statistical significance. The other consideration is that recovery from ATN involves de-differentiation and proliferation of renal tubular epithelium [29]. Active vitamin D has significant anti-proliferative and pro-differentiation actions and it is possible that lower levels of 1,25(OH)$_2$D allow for faster recovery from life threatening AKI. Conversely, higher levels can be associated with prolonged AKI and worse outcome.

There are several limitations to our study. Our study is very small and observational and cannot ascribe causality. Other weaknesses include lack of critically ill patients without AKI as comparators, the variation in sample collection time from onset of AKI, and the lack of measurement of FGF-23 levels. The mortality for patients in this study was 30%, lower than the anticipated 40-50% in a similar population. The strength of the relationship of 1,25(OH)$_2$D to mortality is relatively low (p=0.046), and could be spurious and explained by a type I error.

In conclusion, 25-OH vitamin D levels and 1,25(OH)$_2$D levels were significantly lower in patients with AKI compared to healthy controls. In-hospital mortality was associated with higher 1,25(OH)$_2$D levels compared to survivors, but this effect was not seen on multivariate regression analysis despite controlling for and Apache II. This is a small pilot study and a larger study is required to evaluate the relationship of 1,25(OH)$_2$D to outcomes in AKI.

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