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Absence of adynamic bone disease in African-Americans with CKD Stage 5 after 3 years of vitamin D therapy guided by iPTH and the PTH-(1-84)/N-terminally truncated PTH fragments ratio

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Key words
intact PTH – PTH ratio – vitamin D therapy – adynamic bone disease

Abstract. Background: Secondary hyperparathyroidism is a frequent complication of chronic kidney disease (CKD). The goal of treatment is to achieve circulating levels of parathyroid hormone (PTH) associated without oversuppression of bone turnover. This is commonly achieved by treatment with vitamin D analogs. Doses of vitamin D compounds are usually monitored by measurement of circulating levels of PTH. Study design: To prospectively assess the effects on bone histology of two different protocols for dosing vitamin D. Setting and participants: African-American patients from the same geographic area, managed by the same team of physicians in three dialysis clinics were studied. Patients were treated with vitamin D for 3 years and underwent bone biopsies for assessment of bone turnover. Dosing of vitamin D during the 3 years prior to the biopsy was done following two different guidelines. One group was treated following K/DOQI guidelines adapted to the bio-intact PTH assay (Protocol A), the other group was managed (Protocol B) following K/DOQI guidelines for intact PTH and/or the ratio of PTH-(1-84)/N-terminally truncated fragments (PTH ratio). Predictor: Levels of circulating PTH and/or PTH ratio. Outcome: Prevalence of low bone turnover. Measurements: Qualitative and quantitative assessment of bone histology after tetracycline labeling. Results: 7 out of 22 patients managed following Protocol A were found to have low bone turnover (32%) by bone histology. None of the 21 patients managed by Protocol B for guidance of vitamin D therapy, had low bone turnover. Limitations: Lack of bone biopsy at the beginning of study. Conclusions: This report indicates that the additional information provided by the PTH ratio represents a distinct advantage in avoiding low bone turnover over the use of a single PTH assay to guide vitamin D dosing in African-American patients with CKD Stage 5 on dialysis.

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Introduction

Secondary hyperparathyroidism occurs early in the development of chronic kidney disease (CKD) [Gutierrez et al. 2008, Lehmann et al. 2008, Malluche et al. 1976] and results in bone disease characterized by various degrees of increased bone turnover. The most commonly employed treatment of secondary hyperparathyroid bone disease is vitamin D therapy, which has been shown to have positive effects on renal osteodystrophy [Goldstein et al. 1980, González 2008, Indridason and Quarles 2000, Malluche et al. 1980, Mochizuki et al. 2007, Staniforth et al. 2005] and patient survival [Kalantar-Zadeh et al. 2006, Kovesdy et al. 2008, Melamed et al. 2006, Shoji et al. 2004, Teng et al. 2003, 2005, Tentori et al. 2006]. However, overdosing of vitamin D therapy carries the undesirable risk to induce over-suppression of bone turnover [Baker et al. 1989, Goodman et al. 1994, Kazama et al. 2005, Salusky et al. 1998]. It is therefore of utmost importance to provide a carefully guided course of vitamin D treatment to CKD-5 patients. The intact parathyroid hormone assay (iPTH) is widely used as a surrogate for bone biopsy in the di-

agnosis of renal osteodystrophy [Andress 2005, Goodman 2007, Hernandez et al. 2005, Salusky et al. 2003]. However, studies have shown that the iPTH assay in fact measures both PTH-(1-84) and N-terminally truncated fragments which have opposing biological actions. More recently, the Bio-Intact™ PTH (bio-PTH) assay was introduced, which measures only PTH-(1-84) and has been used routinely and interpreted as approximately half the value of the intact PTH assay value [Salusky et al. 2003]. Subtraction of PTH-(1-84) from the intact PTH results allows to calculate the N-terminally truncated fragments. It was proposed that the ratio between PTH-(1-84) and the fragments (PTH ratio) is a better indicator of bone turnover than PTH-(1-84) or intact PTH [Monier-Faugere et al. 2001].

African-American patients are of particular interest with respect to vitamin D therapy because of the known difference in blood levels of PTH between African-Americans and white patients [Bell et al. 2001, Fuleihan et al. 1994]. It has been demonstrated that the average level of iPTH is higher in African-American patients with pre-dialysis CKD [Gutierrez et al. 2008] and CKD-5 on dialysis [Gupta et al. 2000, Wolf et al. 2007] compared to their white counterpart. African-American CKD-5 patients constitute 29% of the total CKD population in the US and the incidence of CKD-5 among African-Americans is nearly 3 times that of white CKD-5 patients [US Renal Data System 2006]. Current K/DOQI guidelines [K/DOQI Clinical Practice Guidelines 2003] do not discern between African-Americans and white patients. Studies using bone biopsies have shown that the average iPTH value for African-American CKD-5 patients with adynamic bone disease is the same as in white patients with high bone turnover disease [Sawaya et al. 2003]. This calls for an alternative guideline for African-American CKD-5 patients to the standard guideline of an iPTH range of 150 – 300 pg/ml in order to prevent oversuppression of parathyroid glands. This issue has great clinical relevance since adynamic bone disease, which is on the rise [Malluche et al. 2004, Malluche and Monier-Faugere 1992, Monier-Faugere and Malluche 1996], is associated with arterial calcification in CKD-5 patients [Adragao et al. 2006, Blacher et al. 2001, London et al. 2004] and increased morbidity/mortality [Block et al. 2004, 2007, Stevens et al. 2004].

The study tested the hypothesis that using the PTH ratio, which informs on the relative quantity of active PTH-(1-84) and antagonist PTH-(7-84), in addition to intact PTH instead of PTH alone following the K/DOQI for guidance of vitamin D dosing will result in lower prevalence of adynamic bone disease.

Table 1. Demographic characteristics at time of bone biopsy in 43 CKD Stage 5 patients following two different protocols for vitamin D dosing.

	Protocol A (n = 22)	Protocol B (n = 21)	p values
Age (years)	57.0 ± 2.26	50.3 ± 2.60	0.074
Sex (m/f)	13/9	9/12	0.366
Dialysis vintage (months)	33 ± 6	37 ± 5	0.826
Diabetics (%)	31.8	33.3	1.000
Phosphate binders			0.819
Sevelamer hydrochloride	14	15	
Calcium acetate	6	3	
Sevelamer + calcium	2	0	
No phosphate binder	0	3	

Patients and methods

Study design

The study was designed as a prospective cross-sectional study. Effects of implementation of two different protocols for dosing active vitamin D for PTH management and resulting bone histology changes after 3 years were studied. The study was approved by the Henry Ford's IRB and the study was conducted in adherence with the Declaration of Helsinki.

Patients

Patients were recruited from three dialysis clinics of the same geographic area. Patients were seen by the same team of physicians following the same standard management policies with exception of monitoring of vitamin D therapy. Details on patient demographics who underwent bone biopsy are shown in Table 1.

Table 2. Vitamin D dosing protocols.

Dosing	Protocol A	Protocol B
Reduce dose if:	bio-PTH < 75 pg/ml	iPTH < 150 pg/ml OR PTH ratio < 1.4
Maintain dose if:	bio-PTH = 75 – 150 pg/ml	iPTH = 150 – 300 pg/ml AND PTH ratio > 1.4
Increase dose if:	bio-PTH > 150 pg/ml	iPTH > 300 pg/ml AND PTH ratio > 1.4

Note: to convert blood PTH from pg/ml to ng/l, multiply by 1.

Inclusion and exclusion criteria

Inclusion criteria were chronic maintenance hemodialysis patients of African-American ethnicity, ages 18 – 80 years on vitamin D therapy. Exclusion criteria were patients with iPTH less than 100 pg/ml, during the past 6 months, treatment with cinacalcet HCL, steroids or other immunosuppressive agents or change in dose of vitamin D of more than 50%. In addition, patients were excluded who had previously undergone a parathyroidectomy or were known to have malignancy. Patients who qualified and agreed to participate in the study signed informed consent form in the presence of a witness.

Vitamin D dosing

Vitamin D dosing was done following two different protocols (Protocols A and B) as shown in Table 2. Vitamin D dosing was reduced if bio-PTH levels were less than 75 pg/ml (Protocol A) or iPTH levels were less than 150 pg/ml or PTH ratio was less than 1.4 (Protocol B). Vitamin D doses were maintained if bio-PTH was between 75 and 150 pg/ml (Protocol A) or iPTH was between 150 and 300 pg/ml and PTH ratio > 1.4 (Protocol B). Increase in vitamin D dosing was instituted if bio-PTHI was > 150 pg/ml (Protocol A) or iPTH > 300 pg/ml and PTH ratio > 1.4. The threshold levels of bio-PTH were calculated based on the K/DOQI guidelines and the fact that it was shown that iPTH levels are approximately 50% higher than levels measured by bio-PTH [Salusky et al. 2003]. In addition, dosages of vitamin D were adjusted based on monitoring of serum calcium, phosphorus and calcium × phosphate product levels following K/DOQI guidelines. Paricalcitol was the vitamin D analog used in all patients with the exception of 1 patient in Protocol A and 2 patients in Protocol B patients who were treated with calcitriol.

Biochemical and PTH assays

Blood samples were obtained on the day of bone biopsy in the fasting state. Serum calcium and phosphorus were measured by routine laboratory techniques. Serum bone-specific alkaline phosphatase levels were measured using an immunocapture enzyme activity assay (Metra BSAP EIA kit). The normal range of the assay is 11.6 – 29.6 U/l for premenopausal women; 14.2 – 42.7 U/l for postmenopausal women; and 15.0 – 41.3 U/l for men. The intra- and inter-assay coefficients of variation are < 6% and < 8%, respectively.

For PTH measurements, blood was collected in ethylenediaminetetraacetic acid (EDTA), evacuated collection tubes, inverted gently 5 times and centrifuged at 500 × g for 10 – 15 minutes. All samples were processed into plasma within 60 minutes of blood collection. Plasma was then aliquoted into cryovials and stored at –20 ºC until the time of the PTH assay(s). PTH was measured according to the manufacturer's instructions using either the Bio-Intact™ PTH Assay (Nichols Institute Diagnostics, San Clemente, CA, USA) or the Total Intact PTH™ Assay (tPTH) and the 1-84 Whole PTH (CAP™ Assay values (Scantibodies Laboratory, Santee, CA, USA). The N-terminally truncated PTH fragments were calculated by subtracting PTH-(1-84) from the total PTH. The PTH ratio was calculated by dividing PTH-(1-84) by the N-terminally truncated PTH fragments. For Bio-Intact PTH assay the intra- and

Table 3. Biochemical and hormonal results at time of bone biopsy in 43 CKD Stage 5 patients following two different protocols for vitamin D dosing.

	Protocol A (n = 22)	Protocol B (n = 21)	p values
Serum calcium (mg/dl)	8.86 ± 0.09	9.0 ± 0.14	0.481
Serum phosphorus (mg/dl)	4.94 ± 0.26	5.56 ± 2.51	0.123
Serum calcium x phosphorus product	43.9 ± 2.49	50.2 ± 2.51	0.146
Serum bone-specific alkaline phosphatase (U/l)	25.8 ± 2.70	45.3 ± 3.94*	0.001
Plasma PTH levels (pg/ml) Total PTH Whole PTH PTH ratio Bio-PTH	 612 ± 36.7	 732 ± 101 424 ± 57 1.66 ± 0.19 	
Dose of vitamin D/dialysis session (µg equivalent)	5.77 ± 0.79	3.05 ± 0.39*	0.006

*Significantly different from Protocol A, $p < 0.01$; doses of vitamin D averaged over the 6 months prior to bone biopsy.
Note: to convert serum calcium from mg/dl to mmol/l, multiply by 0.2495; serum phosphorus from mg/dl to mmol/l, multiply by 0.3229; plasma PTH levels from pg/ml = ng/l.

interassay coefficients of variation are 2.2% and 7.6%, respectively, and the normal range is 6 – 40 pg/ml. Intraassay coefficients of variation for the tPTH and CAP assays are 3.77% and 4.0%, respectively. The interassay coefficients of variation are 5.18% and 5.45%, respectively. Normal ranges are 14 – 66 pg/ml and 5 – 39 pg/ml, respectively.

Bone biopsy and mineralized bone histology

Bone biopsies were performed as previously described [Malluche and Monier-Faugere 1994] after 3 years of vitamin D management following the two different protocols. Briefly, for bone labeling, patients received tetracycline hydrochloride at a dose of 250 mg orally, 3 times a day for 3 days, 20 days before bone biopsy. No tetracycline hydrochloride was administered for the following 11 days. A second administration of oral tetracycline hydrochloride (250 mg 3×/d) or demeclocycline hydrochloride (Declomycin®, Lederle, Wayne, NJ, USA) (300 mg 2×/d) was administered for the next 3 days. Bone biopsies were performed 4 days after the last dose of tetracycline. Phosphate binders and other antacids were not given on days of tetracycline administration.

Bone samples were processed without removal of the mineral as previously described [Malluche and Faugere 1986]. Sections were stained with the modified Masson-Goldner trichrome stain [Goldner 1938], the aurin-tricarboxylic acid stain [Lillie and Fullmer 1976], and solochrome azurin [Denton et al. 1984]. Unstained sections were prepared for phase contrast and fluorescent light microscopy. Presence of adynamic bone disease was established by quantitative assessment of activation frequency. Adynamic bone disease was diagnosed when activation frequency was below 0.49 y^{-1} or bone formation rate/bone surface below 1.8 $mm^3/cm^2/y$ and osteoid thickness < 20 µm.

Statistical methods

Results are expressed as means ± SEM. Comparison of categorical variables between the two protocols was made using the Fisher's exact test. Comparison between continuous variables was made using the Mann-Whitney U-test. Correlation coefficients between histomorphometric parameters of bone and PTH results were computed using the Spearman test. Multivariate associations were assessed using logistic regression analysis to determine the effects of protocol or vitamin D dose on low bone turnover, adjusted for age,

Table 4. Static and dynamic histomorphometric of bone in 43 CKD Stage 5 patients following two different protocols for vitamin D dosing.

Histomorphometric parameters of bone	Protocol A (n = 22)	Protocol B (n = 21)	Normal values
Bone volume/tissue volume (%)	24.2 ± 1.76	26.2 ± 2.00	16.8 – 22.9
Trabecular thickness (μm)	124 ± 6	133 ± 8	99 – 142
Trabecular separation (μm)	429 ± 37	396 ± 32	280 – 658
Osteoid volume/bone volume (%)	4.57 ± 0.69	9.49 ± 1.00**	0.57 – 6.0
Osteoid surface/bone surface (%)	25.1 ± 2.52	40.8 ± 2.59**	3.45 – 37.9
Woven osteoid surface/osteoid surface (%)	3.54 ± 1.36	10.4 ± 2.46**	0
Osteoid thickness (μm)	10.5 ± 0.63	14.3 ± 0.87**	4 – 20
Number of osteoblasts/bone perimeter (#/100 mm)	184 ± 44.7	593 ± 118**	1 – 200
Erosion surface/bone surface (%)	6.85 ± 1.33	10.3 ± 1.28**	0.1 – 5.69
Erosion depth (μm)	18.0 ± 1.60	25.8 ± 2.38*	4.3 – 7.3
Number of osteoclasts/bone perimeter (#/100 mm)	71.9 ± 14.5	105 ± 14.4**	0.1 – 53
Fibrosis surface/bone surface (%)	3.65 ± 1.00	11.5 ± 3.15**	0
Mineral apposition rate (μm/d)[a]	1.00 ± 0.10	1.26 ± 0.09*	0.36 – 0.63
Mineralizing surface/bone surface (%)[a]	8.54 ± 1.42	12.6 ± 1.16*	4 – 12
Bone formation rate/bone surface ($mm^3/cm^2/yr$)[a]	3.84 ± 0.59	5.79 ± 0.68*	1.80 – 3.08
Mineralization lag time (d)[a]	44.5 ± 7.38	56.3 ± 9.35	< 50
Activation frequency (y^{-1})[a]	0.81 ± 0.14	1.06 ± 0.10*	0.49 – 0.72

[a]n = 16 for Protocol A and n = 18 for Protocol B. *Significantly different from Protocol A, $p < 0.05$. **Significantly different from Protocol A, $p < 0.01$.

duration on dialysis, and diabetes. Computations and analyses were performed using SPSS 7.5 software package for Windows (SPSS, Inc., Chicago, IL, USA).

Results

43 patients fulfiled the selection criteria and agreed to participate in the study. The patients from the two protocols who underwent bone biopsies were comparable with respect to age, sex, dialysis vintage and diabetic status (Table 1). Also there were no significant differences in serum calcium and phosphorus levels and calcium × phosphate products at time of biopsy between the two protocols (Table 3). Using the PTH ratio as a guide for therapy (Protocol B) resulted in an overall lesser vitamin D dose administered, averaged over the 6 months prior to biopsy (Table 3). In Protocol A, 7/22 patients (32%) were found to have adynamic bone disease. In contrast, in Protocol B, where therapy was guided by the PTH ratio in combination with iPTH, no adynamic bone disease was found. The difference in prevalence of adynamic bone disease between the two protocols was statistically significant ($p < 0.01$). Parameters of bone structure were not different between the two protocols (Table 4), however, static and dynamic parameters of bone turnover were significantly higher in patients treated with vitamin D following Protocol B than in patients of Protocol A. There were no correlations between any of the PTH results and static and dynamic parameters of bone turnover (r ranging from 0.05 – 0.36). Moreover, there was no difference in PTH levels when patients were classified as having low, normal or high bone turnover in Protocol A or between normal and high bone turnover in Protocol B (Figure 1). Comparison between patients with adynamic bone disease and patients with normal or high bone turnover followed by Protocols A and B did not show differences in prevalence of factors known to be associated with adynamic bone disease.

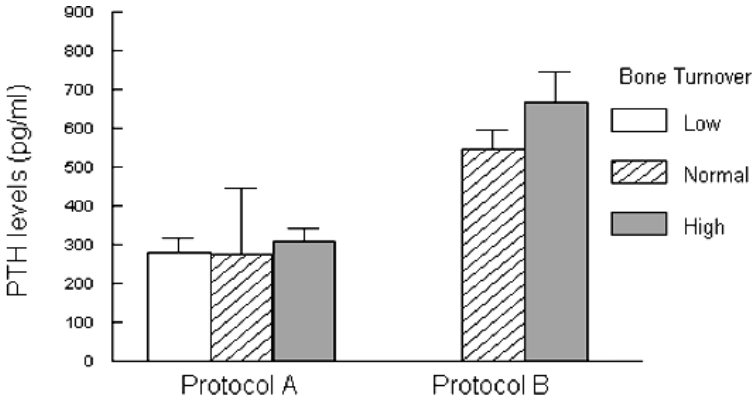

Figure 1. Plasma PTH concentrations at time of bone biopsy in patients with low, normal, or high bone turnover following Protocols A and B for vitamin D dosing. Protocol A used bio-PTH levels for guidance of vitamin D therapy. Protocol B used iPTH and/or PTH ratio for guidance of vitamin D therapy.

These include age, sex, diabetes, dialysis vintage, phosphate binders, and serum calcium and phosphorus levels. When all patients were pooled, logistic regression showed that low bone turnover was predicted by protocol, and not vitamin D dose.

Discussion

The present study shows that following the PTH ratio together with intact PTH is superior to following results of one PTH assay alone for monitoring vitamin D dosing in preventing development of adynamic bone disease.

For African-American hemodialysis patients, who make up 29% of the total dialysis population [US Renal Data System 2006], the average intact parathyroid hormone (iPTH) values for adynamic bone disease have been demonstrated to be 3 times higher than iPTH values for white patients with adynamic bone disease or equivalent to the iPTH values for high bone turnover disease for white hemodialysis patients [Sawaya et al. 2003]. It is, therefore, difficult to apply the K/DOQI-based treatment guidelines for African-American CKD-5 patients and avoid inappropriate dosing of vitamin D. The K/DOQI guidelines were based on results from patient studies in which information on race was not available [Cannella et al. 1994, Carmen Sanchez et al. 2000, Dressler et al. 1995, Frazeo et al. 2000, Fukagawa et al. 1994, Llach et al. 1995, Quarles et al. 1992, Solal et al. 1991, Sprague and Moe 1992]. It was shown that although African-Americans exhibited higher overall PTH values compared to white hemodialysis patients, the PTH-(1-84)/PTH-(7-84) ratio was lower, indicating a higher proportion of PTH-(7-84) in the African-American versus white CKD-5 patient [Fehmi et al. 2006]. Since PTH-(7-84) has been shown to antagonize the effects of PTH-(1-84) on calcium and bone turnover [Langub et al. 2003, Nguyen-Yamamoto et al. 2001, Slatopolsky et al. 2000], this might explain, at least in part, why with higher levels of circulating PTH, bone does not show a commensurate increase in bone turnover. The present study confirms a previous report that showed lack of correlation between PTH levels and static and dynamic histomorphometric parameters of bone turnover in African-American CKD-5 patients [Sawaya et al. 2003]. This explains the lack of differences in PTH levels between patients with various levels of bone turnover. Moreover, vitamin D treatment may have had a confounding effect on bone turnover and could have overridden the effects of PTH in the studied African-American patients [Malluche et al. 1986].

In Protocol A, a higher amount of vitamin D analog was used. The mean dose of vitamin D administered per hemodialysis session (averaged over the 6 months prior to bone biopsy) in Protocol B was 3.5 ± 0.39 μg, whereas, in Protocol A 5.77 ± 0.79 μg were given. However, in the multivariate analysis, the average vitamin D dose was not an independent factor in the prediction of adynamic bone disease. Serum levels of 25 or 1,25 vitamin D were not measured but it can be assumed that circulating vitamin D concentrations were larger in Protocol A. It has been shown that excessive vitamin D administration may lead to oversuppression of bone turnover [Baker et al. 1989, Goodman et al. 1994, Malluche and Monier-Faugere 1992]. The current study cannot definitively establish a cause and effect relationship between vitamin D and adynamic bone disease, but no other factor could be identified for the adynamic state.

A previous study [London et al. 2004] has helped to clarify the specific morbid effects associated with excessive lowering of para-

thyroid activity. Using bone biopsies and arterial calcification scoring, it was shown that adynamic bone disease is associated with arterial calcification in CKD-5 patients, as opposed to hyperparathyroidism. This was a critical finding in light of a separate study conducted in 2001 [Blacher et al. 2001] that disclosed a correlation between arterial calcification and CKD-5 patient mortality. The high incidence of soft tissue calcification associated with chronic dialysis was reported more than 30 years ago [Ritz et al. 1974] and has since been confirmed by other studies [Goodman et al. 2000]. Autopsy results revealed that dialysis patients exhibit twice the amount of the soft tissue calcification of non-dialysis patients [Kuzela et al. 1977]. It was also shown that in the first year of dialysis, there is a correlation between higher PTH ratios and survival [Tamez et al. 2007].

One limitation of the study is that no bone biopsies were performed before introducing the two different vitamin D dosing protocols. However, the finding of absence of adynamic bone disease in vitamin D-treated African-American CKD-5 patients who are known to have generally lower bone turnover than their white counterpart has never been observed before. Prevalence of adynamic bone disease in unselected dialysis population was reported to be approximately 40% [Ferreira et al. 2008, Malluche et al. 2004, Pei et al. 1995].

This report indicates that the additional information provided by the PTH ratio represents a distinct advantage in avoiding low bone turnover over the use of a single PTH assay to guide vitamin D dosing in African-American patients with CKD Stage 5 on dialysis.

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Conflict of interest

Tom Cantor is president of Scantibodies Laboratory. All other authors declare no conflict of interest.

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