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Racial differences in bone histomorphometry in Children and Young Adults treated with Dialysis

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Abstract

Background—Healthy African-Americans are known to have greater bone mineral density and decreased risk of fracture when compared to Caucasians. In fact, comparisons of bone histomorphometry in healthy South African children and adults reveal greater cortical thickness in Black subjects as compared to White. How these differences are reflected in the bone of American children and young adults on dialysis is unknown.

Methods—Using tetracycline-labeled, iliac crest bone biopsies obtained in prior research protocols in pediatric and young adult dialysis patients, we compared trabecular and cortical parameters between non-Hispanic African-American subjects and non-Hispanic Caucasian subjects matched by age and gender. A linear regression model controlled for trabecular turnover and mineralization was used to further investigate the association of race with cortical thickness.

Results—The matched cohort consisted of 52 subjects-26 African-American and 26 Caucasian. Turnover, mineralization and volume parameters in trabecular bone did not show significant differences between racial groups. Characterizing subjects by renal osteodystrophy type did not show a statistically significant difference although Caucasian patients had double the prevalence of mineralization defects. Consistent with this was a trend toward better mineralization parameters in African-Americans including shorter osteoid maturation time and lower osteoid volume. A sub-cohort of patients with cortical measures demonstrated greater median (IQR) cortical thickness in African-Americans (541μm [354, 694]) than in Caucasians (371μm [336, 446], p=0.08). In a linear regression model controlling for trabecular turnover and mineralization, African-American subjects had 36.2% (95% CI 0.28 to 85.1%, p=0.048) greater cortical thickness as compared to White subjects. There was no significant difference in cortical porosity.

Conclusions—Although likely limited by sample size, our findings suggest that, similar to findings in populations of normal children, African-American race in pediatric and young adults on dialysis is associated with greater cortical thickness. Additionally, there was a trend toward

greater mineralization defects in Caucasian children. Both findings require further exploration with larger patient samples in order to thoroughly explore these racial differences and the implications on CKD-MBD treatment.

1.1. INTRODUCTION

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) is the major co-morbidity affecting children and adults with chronic kidney disease. This entity is characterized by abnormalities in calcium-phosphate balance, parathyroid hormone, Vitamin D as well as an early increase in fibroblast growth factor 23 (FGF23)[1]. The skeletal consequences of these abnormalities are termed renal osteodystrophy and iliac crest bone biopsy is the gold standard for the characterization of these lesions that encompass abnormalities in bone turnover, mineralization and volume. These abnormalities develop early in the CKD course, even as early as CKD stage 2, and become increasingly more abundant with CKD progression [2]. Ultimately, these abnormalities result in delayed growth, increased fracture risk and boney deformities in adult and pediatric patients [3]. The current therapeutic approach to the management of renal osteodystrophy assumes a standard response of bone to the perturbations associated with CKD [4]. However, there are potential flaws in this assumption, with one flaw being the lack of attention to racial differences in bone metabolism. Racial differences in bone have been demonstrated in populations of healthy children in which African-American children show greater pubertal bone mineral density accrual and greater bone strength [5, 6]. Paradoxically, evidence of greater bone density in African-Americans is apparent despite having higher PTH levels and greater rates of Vitamin D deficiency [6, 7]. Similar findings have also been described in healthy adult individuals and in patients across the spectrum of CKD including those treated with dialysis. For instance, African-American adult patients treated with dialysis have demonstrated decreased rates of fracture, including hip fracture, when compared to Caucasian dialysis patients [8, 9]. Furthermore, iliac crest bone biopsy studies have demonstrated greater preservation of cortical thickness in those subjects considered to be of Black race [10–12]. Despite these findings, little is known of how racial background impacts bone histomorphometry in pediatric patients with CKD. Therefore, the current study was designed to assess whether there are differences in trabecular and cortical bone by racial background within a group of pediatric and young adult patients treated with dialysis.

1.2 METHODS

1.2.1 Patient Population

We analyzed the pre-treatment (baseline) bone histomorphometry results in patients who were receiving maintenance dialysis and underwent tetracycline-labeled iliac crest bone biopsies under research protocols exploring the spectrum of renal osteodystrophy [13–15]. All subjects underwent a 2-week washout period from active Vitamin D sterols prior to the performance of the bone biopsy as we have previously reported [16]. 26 Caucasian (non-

Hispanic) subjects were matched with 26 African-American (non-Hispanic) subjects by age and gender. When a choice existed between potential matches, the match with the most similar PTH level was chosen. Disease etiology was categorized as congenital anomalies of the kidney and urinary tract (CAKUT), glomerulonephritis (GN) and other/unknown. The majority of the other/unknown category was unknown which refers to patients whose clinical presentation did not allow for a definitive diagnosis. Dialysis modality was defined as either hemodialysis (HD) or peritoneal dialysis (PD) at the time of bone biopsy. The study was approved by the UCLA Human Subject Protection Committee. All patients 18 and older provided signed informed consent and those younger than 18 years had informed consent signed by their legal guardian.

1.2.2   Bone histomorphometry

Full detail of the iliac crest procedure and histomorphometric analysis can be obtained from the reference by Hernandez et al [16]. In brief, full-thickness bone biopsies were obtained from the anterior iliac crest (2 cm below the anterior superior iliac spine) using a modified Bordier trephine needle after double-tetracycline labeling, as previously described [16]. Biopsy specimens were 0.5 cm in diameter $\times$ 1–2 cm in length. Specimens were dehydrated in alcohol, cleared with xylene, and embedded in methyl methacrylate. Static histomorphometric parameters were evaluated in undecalcified 5-μm sections treated with modified Masson– Goldner trichrome stain; tetracycline labeling was assessed in unstained 10-μm sections. Cortical bone was identified by its compact structure containing several osteons in an eccentric position and Sharpey fibers. These structures are very easy to identify under microscopy especially when polarized light is applied. The distinction between cortical and cancellous bone can be difficult in some cases specifically in patients with high turnover diseases. Thus, if the cortical bone completely lost its compact structure and only cancellous bone was observed, we considered the cortical to be completely trabeculated and no measurement was performed. The cortical width was defined as the distance between the periosteal surface and the endocortical surface of each cortex (Figure 1). At the time of iliac crest bone biopsy, the soft tissue on cortical samples was not preserved; therefore it was not possible to distinguish internal and external cortices. Furthermore, owing to renal failure, the predominance of primary bone as an indicator of external cortex was also not reliable. Therefore, given this difficulty, statistical analysis of cortex was undertaken only in those patients with two pieces of cortex (n=35) [17] and the average of cortical thickness and porosity between cortices was used as the outcomes of interest. Primary bone histomorphometric parameters were assessed in trabecular and cortical bone under 200x magnification using the OsteoMetrics[R]system (OsteoMetrics, Decatur, IL, USA) by histomorphometrist (RCP) blinded to patient identity and biochemical values. Bone pathology in trabecular bone was characterized using the Turnover, Mineralization, and Volume (TMV) classification for renal osteodystrophy [18, 19] and the definitions for derived parameters are available in Appendix A. The TMV system created standardized nomenclature for the assessment of renal osteodystrophy in order to facilitate comparisons between research studies. Skeletal lesions were classified by histomorphometric criteria with reference to values previously established in 27 children with normal renal function between the ages of 2.5 to 17 years who had undergone iliac crest bone biopsy during elective orthopaedic surgical procedures [20, 21]. Skeletal lesion classifications included mild

disease, mixed uremic osteodystrophy, osteitis fibrosa cystica, adynamic bone disease and osteomalacia. At the time of biopsy, the following biochemicals were obtained: calcium, phosphate, PTH and alkaline phosphatase.

1.2.3 Statistical Analysis

All variables for trabecular, cortical and biochemical parameters were assessed for normality using the Shapiro-Wilks test. Normally distributed variables are presented as means +/− SD while non-normally distributed variables are presented as medians (Interquartile Range, IQR). Comparisons between racial groups were made using the paired T-test and Wilcoxon-Signed Rank tests for parametric and nonparametric analyses, respectively. Categorical variables are reported as frequency and percentages. The differences in proportions between racial groups were analyzed using chi-square analysis or Fisher Exact test (for cell sizes less than 5). Multivariate linear regression was used to determine racial differences in cortical thickness for a given degree of trabecular bone involvement. In this model, cortical thickness was $\log_{10}$-transformed to achieve a symmetric distribution. The number of covariates in this model was limited by patient sample size and includes bone formation rate, eroded surface and osteoid maturation time. These turnover parameters were chosen as surrogates of overall PTH activity given this variable was missing in numerous patients. The mineralization parameter was chosen given a previously demonstrated correlation between cortical bone and trabecular osteoid accumulation [22]. Results for $\log_{10}$-transformed cortical thickness are reported as percent differences according to the formula: [(B^10)-1] *100. The number of missing values are as follows: Calcium (19), PTH (12), Phosphate (7), Alkaline Phosphatase (10). Listwise deletion was used to analyze the existing data. For all analyses, the corresponding p-value of less than 0.05 denotes significance. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

1.3 RESULTS

1.3.1 Patient Population

The cohort consisted of 52 patients with a mean (± SD) age of 14.6 (± 4.9). 65.4% of the cohort was male. Peritoneal dialysis (PD) was the most common modality (71.2%). The median (IQR) dialysis duration was 2.4 (0.7, 5) years. Glomerular disease was the most frequent disease etiology (44.2%). There were no statistically significant differences in the baseline characteristics including age, gender, dialysis modality, dialysis duration and disease etiology although HD as a modality and other/unknown as a disease category showed greater frequency in African-American subjects (Table 1).

1.3.2 Biochemical Markers

There was no difference in serum phosphate, albumin-corrected serum calcium, parathyroid hormone (PTH) or alkaline phosphatase (AP) at the time of bone biopsy (Table 2).

1.3.3 Trabecular Bone Histomorphometry

Trabecular parameters of turnover, mineralization and volume did not differ by race (Table 3). Despite this, the distribution of renal osteodystrophy categories is notably different between racial groups, although, this difference fails to reach statistical significance. For

instance, osteitis fibrosa cystica was the most prevelent category of disease within African-Americans (46.2%) while Caucasians showed almost equal prevalence of mixed uremic osteodystrophy (38.5%) and osteitis fibrosa cystica (34.6%), (Figure 2, p=0.4). In comparison, mixed lesions were only seen in 19.2% of African-American children. Given mixed uremic osteodystrophy is the only disorder of mineralization seen in this cohort, the presence of a mineralization defect is twice as high in Caucasians as compared to African-American children. Supportive of these differences in mineralization, though not reaching statistical significance, are trends consistent with better mineralization in African-Americans including lower osteoid volume, shorter osteoid maturation time and almost half the mineralization lag time of Caucasian subjects (Table 3). Overall, the frequency of adynamic bone disease was low affecting only 7.7% of the entire cohort with no difference between racial categories.

1.3.4   Cortical Bone Histomorphometry

Analysis of cortical bone in 35 patients with two available cortices revealed greater median (IQR) cortical thickness in African-Americans (541μm [354, 694]) than in Caucasians (371μm [336, 446], p=0.08, Figure 3). Median porosity was lower in African-American subjects, though, not statistically different (Table 3). A multivariate linear regression model controlling for parameters of trabecular bone including bone formation rate, eroded surface and osteoid maturation time, showed that African-American race was associated with a 36.2% (95% CI 0.28 to 85.1%, p=0.048) higher cortical thickness than Caucasian race. Using the same covariates, African-American race predicted 22% lower cortical porosity but this failed to reach significance (p=0.4).

1.4   DISCUSSION

This study is the first to compare racial differences in trabecular and cortical bone by histomorphometry in a pediatric and young adult dialysis population. Although, we did not demonstrate statistically significant differences in trabecular bone, Caucasian subjects appear to demonstrate a higher prevalence of mineralization defects and worsened parameters of trabecular mineralization. Our findings also demonstrate that, while controlling for the degree of trabecular involvement, African-Americans have significantly greater cortical thickness as compared to Caucasian subjects. Consistent with this is the trend toward lower cortical porosity in African-American subjects. Our findings are consistent with bone histomorphometry studies in healthy children who have undergone illiac crest bone biopsy. For instance, Schniztler et al. demonstrated greater cortical thickness and decreased cortical porosity in healthy Black South African children when compared to White children [12]. These findings were similarly demonstrated in healthy South African adults [11]. Within the CKD population, Malluche et al. demonstrated that African-American adults undergoing maintenance dialysis had a higher prevalence of normal and high cortical thickness and a lower prevalence of low cortical thickness than Caucascian patients. Contrary to our findings, Malluche et al. demonstrated that African-Americans had a greater prevalence of high cortical porosity than Caucasians [10].

The relative preservation of cortical thickness in young African-American subjects when compared to Caucasians suggests the possibility of variability in the PTH responsiveness of cortical bone in African-American patients. This possibility is supported by studies of healthy children. For instance, using peripheral quantitative computed tomography (pQCT) in a group of healthy, pre-pubertal African-American and Caucasian children Warden et al. demonstrated greater cortical bone density and greater estimated bone strength within the African-American group [6]. Interestingly, the differences in density and strength occurred despite higher levels of PTH as well as greater Vitamin D deficiency amongst the African-American group of children. Similarly, Gilsanz et al. demonstrated greater pubertal bone mineral density accrual resulting in greater peak bone mineral density amongst African-American adolescent girls [23]. The etiology of these findings is currently unknown but these findings raise the possibility of either resistance of cortical bone to PTH or the presence of a greater anabolic effect of PTH on the cortical bone of African-American children. The former possibility is supported by Cosman et al. who performed studies of adult African-American and Caucasian women and demonstrated a smaller increase in bone resorption markers in African-American women in response to a PTH infusion [24]. Cosman et al. also demonstrated greater conservation of urinary calcium in response to PTH infusion, a finding thought to be an adaptive response to the decreased bone response to PTH. Interestingly, our patient population demonstrated lower albumin-corrected calcium in the African-American population, a finding that could potentially reflect the impact of this decreased responsiveness to PTH on the maintenance of serum calcium. In the setting of end stage renal disease, African-American children would lose the adaptive response of retaining greater urinary calcium in order to maintain serum calcium levels. The possibilty of a greater anabolic response to PTH in African-Americans is also of consideration although there are known limitations in the anabolic action of PTH owing to the non-pulsatile nature of PTH elevations in CKD [25].

The previously described differences in bone structure may appear to be protective for African-Americans and likely do provide protection against osteoporosis and fracture risk in the healthy population. Still, critical consideration of these differences is needed in order to determine the implications, if any, on patients with CKD-MBD. For instance, potentially owing to greater PTH resistance, studies in adults undergoing maintenance dialysis have demonstrated the presence of adynamic bone disease at higher PTH levels in African-Americans than in Caucasians. Thus, the favorable PTH resistance of the healthy popualtion, may place African-American patients with CKD at risk for adynamic bone disease when active Vitamin D sterols are used to achieve PTH control. Therefore, the ideal PTH level to maintain adequate bone turnover remains elusive.

Racial differences in bone may also have implications on the outcomes of Caucasian patients for whom preserved cortical thickness in African-Americans implies greater loss of cortical thickness in Caucasians for a given PTH. In fact, our findings may reflect greater cortical trabecularization amongst the Caucasian population. Consistent with this, Power et al. demonstrated the direct relationship between the proportion of active cortical osteons and increasing cortical porosity, the latter of which contributes to structural weakening [26]. Consistent with the greater, though not significant, cortical porosity of our Caucasian population, in a subanalysis in 27 of our patients with available osteon data, Caucasian

subjects demonstrated a slightly greater proportion of active osteons (58.8% vs. 55.2%, Caucasian vs. African-American). Differences in the number of active osteons between races could lead to differences in cortical trabecularization which may be reflected in our findings of lower cortical thickness and greater cortical porosity within the Caucasian group. Ultimately, these differences potentially underlie differences in bone strength. The possibilty of decreased bone strength in Caucasians is supported by studies of healthy children which show a 2-fold increase in fracture risk in Caucasian children when compared to other racial groups [27]. Similarly, in a study from the Netherlands, metabolic bone disease manifesting as low bone mineral density, disabling bone disease and deformities was highly prevalent in Dutch young adults with a history of CKD in childhood [3]. Still, the exact implications of iliac crest cortical differences on outcomes such as fracture remain elusive given differences in bone architecture between the iliac crest and sites prone to fracture. Still, our findings suggest the need to further assess the role of race in the manifestation of CKD-related bone disease in an effort to avoid both overtreatment and under-treatment of racial groups.

The limitations of this study include its retrospective nature and its limited sample size. Because of the latter, we were likely under-powered to detect differences in trabecular bone parameters between the racial groups. Thus, we cannot definitively conclude that they do not exist. In addition, due to the inherent cortical changes which occur in CKD, we were unable to distinguish internal and external cortices. Although the most conservative practice, the use of the average of the two cortices likely diluted nuanced differences between internal and external cortices. Furthermore, we must acknowledge the imprecise nature of racial-ethnic categories in determining true ancestral lineage. Thus, future studies will need to use more precise measures of true ancestry to more clearly elucidate these differences.

In conclusion, in a pediatric and young adult dialysis population, African-Americans demonstrated greater cortical thickness than Caucasian patients and a trend toward better mineralization. It is important to consider what these differences suggest about racial differences in the skeletal response to CKD-MBD perturbations and eventually, how these differences may impact the treatment of renal osteodystropy. Ultimately, larger, better powered studies with more precise measures of ancestral makeup are needed.

1.7 APPENDICES

ACKNOWLEDGEMENTS

Appendix

Appendix A:

Bone Histomorphometry Indices

Abbreviation	Parameter	Unit	Formula
Turnover			
BFR/BS	Bone Formation Rate/ Bone Surface	$\mu m^3/\mu m^2$/year	MAR × MS/BS × 3.65
ES/BS	Eroded Surface/ Bone Surface	%	(Erosive perimeter/bone perimeter) × 100
Mineralization			
OV/BV	Osteoid Volume/Bone Volume	%	Osteoid area/bone area × 100
O.Th	Osteoid Thickness	μm	(Osteoid area/osteoid perimeter) × 2/1.2
OS/BS	Osteoid Surface/ Bone Surface	%	(Osteoid perimeter/bone perimeter) × 100
OMT	Osteoid Maturation Time	days	O.Th/MAR
MLT	Mineralization Lag Time	days	O.Th/Aj.Ar
MAR	Mineral Apposition Rate	μm/day	(Distance between labels/interlabel period)/1.2
Aj.Ar	Adjusted Apposition Rate	μm/day	MAR × (MS/OS)/100
MS/BS	Mineralized Surface/Bone Surface	%	(Double-label perimeter + 1/2 single-label perimeter)/bone perimeter × 100
Volume			
BV/TV	Bone Volume/Tissue Volume	%	Bone area/tissue area × 100
Tb.Th	Trabecular Thickness	μm	(bone area/bone perimeter) × 2/1.2
Tb.N	Trabecular Number	n/mm^2	BV/TV/Tb.Th × 10
Tb.Sp	Trabecular Separation	μm	(1000/Tb.N) - Tb.Th

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Highlights

- Caucasians have a greater prevalence of mineralization defects.

- African-Americans have 36.2% greater cortical thickness than Caucasians.

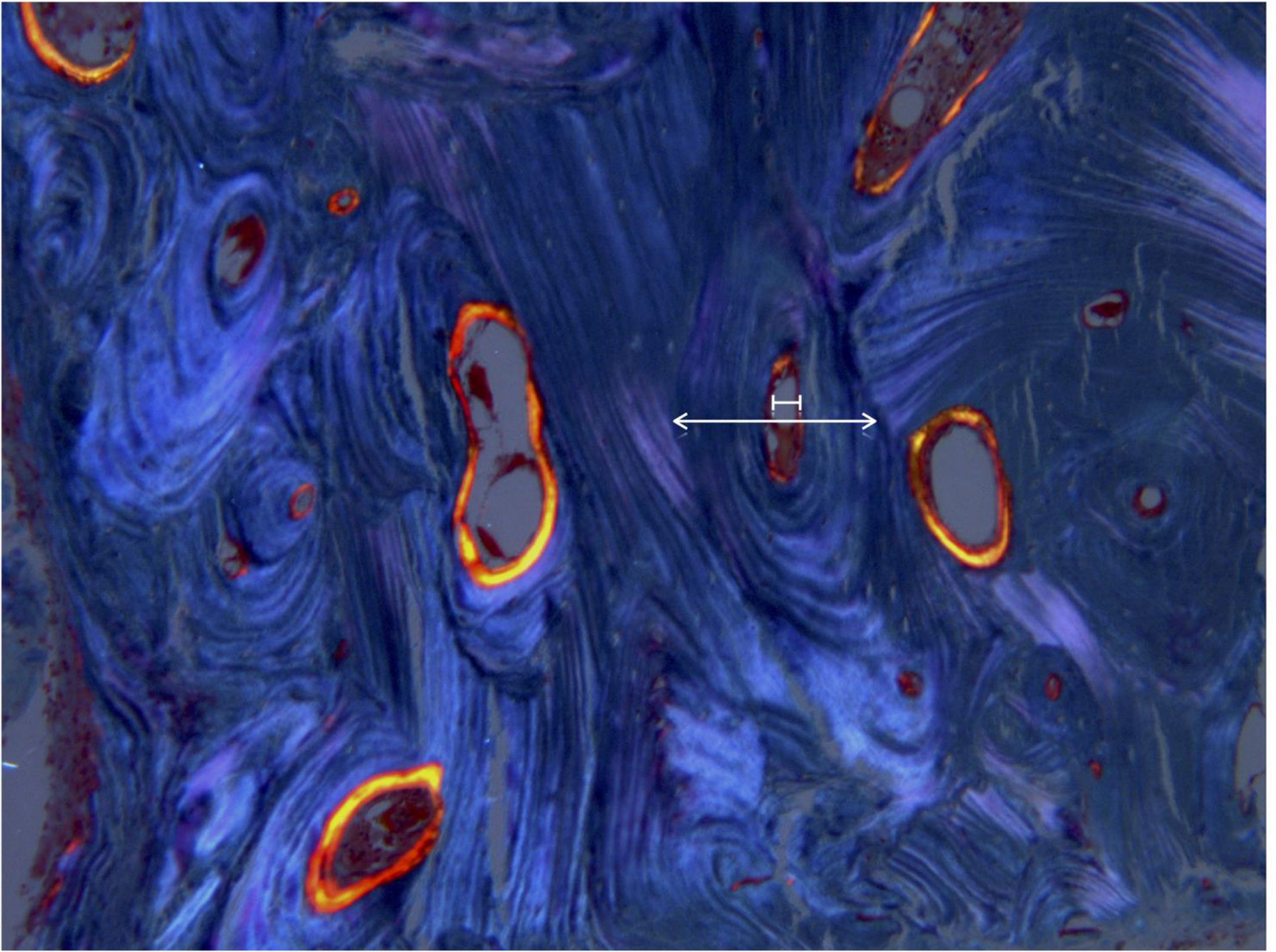- African-Americans demonstrate a trend toward lower cortical porosity.

Figure 1: Example of cortical bone visualized under polarized light.
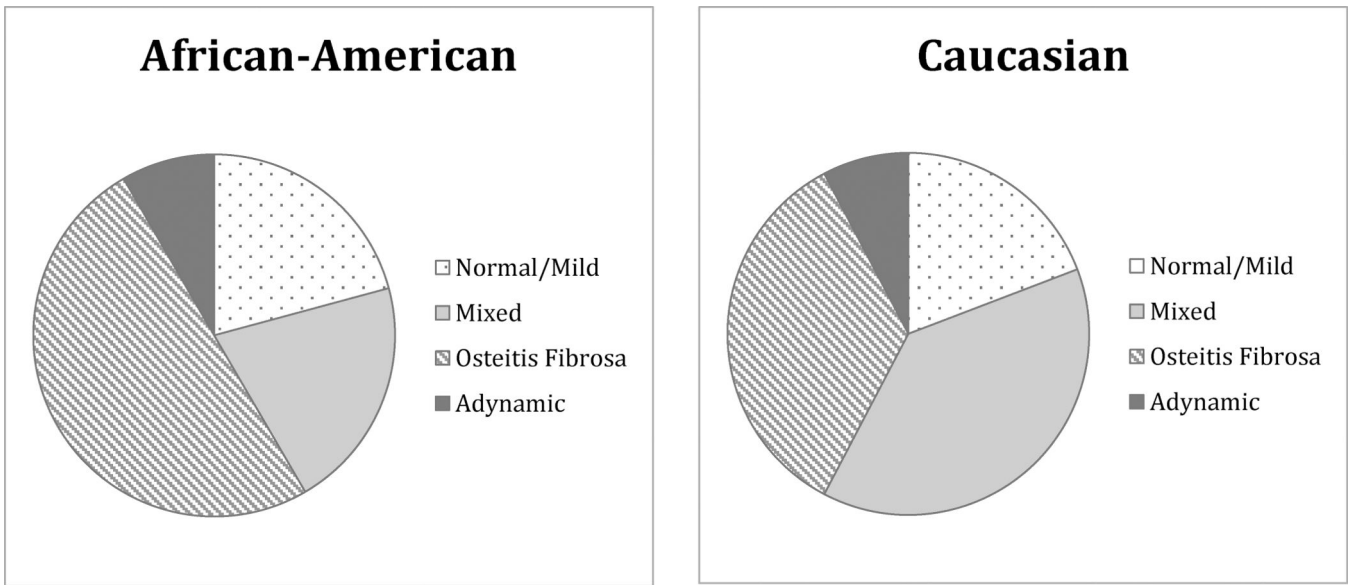The long arrow indicates the osteon diameter and the short line indicates the osteon canal.

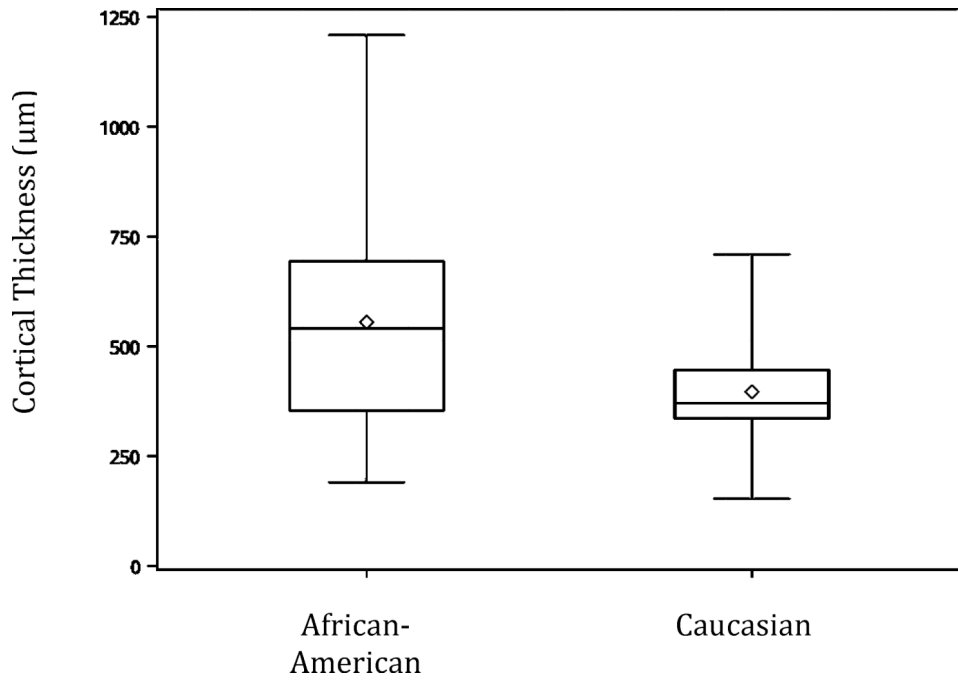**Figure 2: Renal Osteodystrophy Categories by Race**

Figure 3: Median Cortical Thickness by Race

Table 1:

Cohort Characteristics

	African-American	Caucasian	P value
N	26	26	
Age, mean ± SD	14.4 ± 5.1	14.7± 4.7	0.5
Gender, n (%)			1
F	9 (36.6)	9 (34.6)	
M	17 (65.4)	17 (65.4)	
Modality, n (%)			0.2
HD	10 (38.5)	5 (19.2)	
PD	16 (61.5)	21 (80.8)	
Disease Etiology, n (%)			0.2
CAKUT	7 (26.9)	10 (38.5)	
Glomerulonephritis	10 (38.5)	13 (50)	
Other/Unknown	9 (34.6)	3 (11.5)	
Dialysis Duration, yr, median (IQR)	3.2 (1.1, 6.1)	1.3 (0.6, 4.5)	0.7

Normally distributed variables reported as mean (± Standard Deviation) and non-normally distributed variables presented as median (interquartile range).

CAKUT (congenital anomalies of the kidney and urinary tract)

IQR (Interquartile Range)

SD (Standard Deviation)

mg/dL (milligrams per deciliter)

pg/mL (picograms per milliliter)

IU/L (International units per liter)

HD (hemodialysis)

PD (peritoneal dialysis)

Table 2:

Laboratory Values at the time of Biopsy

	African-American	Caucasian	P value
Calcium, mg/dL, mean ± SD	9.1 ± 0.9	9.7 ± 0.9	0.08
Phosphate, mg/dL, mean ± SD	6.5 ± 1.3	6.5 ± 1.5	1
PTH, pg/mL, median (IQR)	681 (352, 1117)	636 (394, 990)	0.1
Alkaline Phosphatase, IU/L, median (IQR)	254 (127, 439)	226 (112, 363)	0.6

Normally distributed variables reported as mean (± Standard Deviation) and non-normally distributed variables presented as median (interquartile range).

IQR (Interquartile Range)

SD (Standard Deviation)

mg/dL (milligrams per deciliter)

pg/mL (picograms per milliliter)

IU/L (International units per liter)

Table 3:

Trabecular and Cortical Bone Parameters by Race

	African-American	Caucasian	Reference Range	P value$^{\$}$
Turnover				
Bone Formation Rate (BFR/BS) ($\mu m^3/\mu m^2$/year)	97.6 ± 65.7	83.5 ± 64.3	8–73.4	0.8
Eroded Surface (ES/BS) (%)	9.8 ± 4.6	8.2 ± 4.2	0.5–4.3	0.2
Mineralization				
Osteoid Volume (OV/BV) (%)	7.2 ± 6.9	9.6 ± 5.9	0.2–5.8	0.2
Osteoid Thickness (O.Th) (μm)	13 ± 6.1	13.8 ± 5.2	2.0–13.2	0.5
Osteoid Surface (OS/BS) (%)	39.9 ± 21.2	47.1 ± 16.4	4.3–37	0.2
Osteoid Maturation Time (OMT) (d)	9.9 (6.5, 13.2)	12.6 (8.9, 20.1)	1.2–11.5	0.07
Mineralization Lag Time (MLT) (d)	16.7 (8.6, 37.8)	34.2 (20.7, 59.8)	2.3–63.8	0.1
Mineral Apposition Rate (MAR) (μm/d)	1.28 (1.1, 1.4)	1 (0.9, 1.3)	1.1–1.5	0.1
Adjusted Apposition Rate (Aj.Ar) (μm/d)	0.8 (0.4, 1.1)	0.6 (0.4, 0.9)	0.14–1.2	0.1
Mineralized Surface/Bone Surface (MS/BS) (%)	20.5 ± 12.3	20.5 ± 11.8	2.2–19	0.6
Volume				
Bone Volume (BV/TV) (%)	33.2 ± 7.8	31.2 ± 9.3	8.9–34.4	0.7
Trabecular Thickness (Tb.Th) (μm)	169.2 ± 35.5	152.8 ± 31.5	91–175	0.2
Trabecular Number (Tb.N) (n/mm^2)	2 ± 0.3	2.1 ± 0.5	91–175	0.3
Trabecular Separation (Tb.Sp) (μm)	342.8 ± 80.6	361.3 ± 171.4	351–737	0.9
Cortical [*#]				
Cortical Thickness (Ct.Th) (μm)	541.1 (354.2, 693.9)	371 (336.2, 446.4)	NA	0.06
Cortical Porosity (Ct.Po) (%)	7.6 (4.6, 17.1)	9.4 (3.4, 11.3)	NA	0.5

Normally distributed variables reported as mean (± SD) and non-normally distributed variables presented as median (interquartile range).

$^{\$}$p value for the comparison between African-American and Caucasian subjects

[*]Cortical analysis performed in sub-cohort of 35 patients with two cortices available.

[#]Cortical norms unavailable from control population.

NA: not available