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REVIEW

Precision Renal Osteodystrophy: What's Race Got to do With It?

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Abstract

Purpose of Review To present race and ethnicity as evidence of the need for precision medicine in renal osteodystrophy.
Recent Findings Previously described racial-ethnic differences in bone persist in recent data on fracture risk in the healthy and CKD populations. These differences have historically been noted between Black and White participants, but recent data suggests racial-ethnic differences in bone are more intricate than previously recognized. A reflection on skeletal differences within the general, non-CKD population, provides a context to better understand skeletal differences by race within CKD.
Summary Despite numerous studies demonstrating racial differences in skeletal microarchitecture, fracture risk and skeletal biomarkers, further evidence is needed to pinpoint the etiology of racial differences and to allow precision treatment that reflects the individual patient, regardless of race. In the end, race is currently our most saliant example of the need for a precision medicine approach to the treatment of renal osteodystrophy.

Keywords Osteodystrophy · Kidney failure · Race

Introduction

Renal Osteodystrophy (ROD) is a critical co-morbidity of chronic kidney disease (CKD) that contributes to skeletal morbidity including fractures, deformity and debility in both children and adults [1]. It is defined by a combination of abnormalities in bone turnover, bone mineralization and bone volume that result from the mineral and hormonal abnormalities of CKD [2]. Renal osteodystrophy diagnosis and categorization is a histopathological diagnosis made by iliac crest bone biopsy. Using fluorescent labeling, categories of bone disease are distinguishable from normal bone and include states of high turnover with fibrosis (osteitis fibrosa), high turnover with abnormal mineralization (mixed disease), low turnover with normal mineralization (adynamic bone disease), and low turnover with abnormal mineralization (osteomalacia) [2]. Because of the limited availability of iliac crest bone biopsy, current diagnosis of ROD relies largely upon surrogates of bone turnover and mineralization like parathyroid hormone and bone specific alkaline phosphatase. With time, we have come to appreciate that the manifestation of ROD is a heterogeneous process with variability between individuals. The most saliant examples of this heterogeneity are found in racial-ethnic differences in bone histomorphometry, fracture and surrogate markers of ROD [3–5]. Skeletal and biochemical differences by race and ethnicity are not unique to the CKD population. Indeed, they are also demonstrated within the general, non-CKD population and these differences inform our understanding of racial-ethnic associations within CKD. In general, these differences manifest in three major areas: 1) racial-ethnic differences in bone histomorphometry and skeletal microarchitecture, 2) racial-ethnic differences in fracture risk and 3) racial-ethnic differences in biochemical markers including vitamin D and PTH. Continued strides in the understanding of these racial differences may have major implications on the precision treatment of ROD, a disease whose current treatment is dependent upon proper prediction of bone pathology.

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Racial-ethnic Differences in Bone Histomorphometry and Skeletal Microarchitecture

Healthy Population

Racial-ethnic differences in bone within the healthy population inform our understanding of these differences within ROD. Racial differences in the skeleton and skeletal outcomes have largely been described amongst post-menopausal women. Numerous studies have concluded that non-Hispanic Black women have higher bone mineral density and a lower prevalence of osteoporosis than non-Hispanic White, Asian and Hispanic women [6]. But even prior to these later-life differences in osteoporosis, studies of healthy children have shown racial differences in pubertal bone mineral accrual in both the axial and appendicular skeleton between black and white children [7, 8]. In general, pubertal bone accrual is greater in both black girls and boys as compared to white girls and boys and these differences result in a 5–10% higher vertebral bone density, on average, in Black children [8]. Whether these racial differences in bone mineral accrual during childhood contribute to the later risk of osteoporosis remains unknown. Underlying these differences in bone mineral accrual are microarchitectural differences in both trabecular and cortical bone. By high resolution peripheral quantitative computed tomography (HR pQCT) black young women and men demonstrate greater cortical and trabecular thickness and lower cortical porosity when compared to their White counterparts [9]. The latter is a feature of bone strength. In addition, in post-menarchal adolescent female participants matched for body composition, Black participants had greater bone strength profiles including greater volumetric bone mineral density and greater bone strength indices than White adolescent female participants [10]. Aside from Black and White race, microarchitectural studies using quantitative CT have demonstrated differences across a number of racial-ethnic groups [11]. The importance of racial-ethnic diversity to this area of research is evident by racial-ethnic differences seen in fracture. While many studies of the past have described a decreased risk of fracture in Black participants as compared to White participants, close examination of the available data demonstrates a greater propensity toward fracture in those of White race when compared to *most* other races [12, 13]. For instance, in a metanalysis of racial-ethnic differences in fracture, the risk of fracture was lower in Black, Hispanic, and Asian when compared to White populations [13]. Similar findings are seen in children in whom the fracture incidence is lower in not only Black children in comparison to White children but also lower in Hispanic and Asian children when compared to White children [12]. As opposed to the predominant view of a lower fracture risk in Black populations, findings from these two fracture studies suggest a relative fracture propensity within the non-Hispanic White population when compared to other non-White populations. How this fracture risk should be reflected in algorithms such as the Fracture Risk Assessment Tool (FRAX) remains under debate. Whereas ignoring race and ethnicity in the FRAX may appropriately move us toward a more anti-racist medical approach, this approach may increase the risk of exposure to anti-resorptive medications in non-White populations who have demonstrated a lower risk of fracture [14, 15]. Still, the use of race and ethnicity as a biological variable in algorithms like FRAX must be done with great care given the biological basis for the observed differences in fracture remains unproven. This is a critical limitation of such algorithms especially as the global population becomes more admixed and not subject to a single racial-ethnic classification. In the end, the question of whether race and ethnicity belong in the FRAX algorithm must be replaced by the question of what biology is being represented by race and ethnicity and what biomarkers reflect this biology across racial-ethnic identification.

CKD Population

Similar racial-ethnic differences in skeletal microarchitecture have been described in ROD. For instance, in the assessment of ROD by iliac crest bone histomorphometry, Malluche et al. discovered that Black individuals with CKD have a higher prevalence of normal and high bone volume when compared to non-Hispanic White individuals among whom a higher prevalence of low bone volume was seen [3]. Additionally, an overwhelming majority of Black individuals had normal or high cortical thickness whereas low cortical thickness was seen in nearly half of White individuals [3]. This latter point of higher cortical thickness has also been demonstrated within a pediatric dialysis population of age, gender, and PTH-matched Black and White children. In this population, Black children had 36.2% higher cortical thickness than White children despite no statistically significant differences in trabecular bone [16].

Also, like the healthy population, racial differences in fracture have been reported in both adult and pediatric CKD populations. The most recent study of racial differences in fracture is within the Chronic Renal Insufficiency Cohort (CRIC). CRIC is a study of adult CKD which demonstrated Black race is a protective factor against hip and vertebral factors [5]. Similarly, Black and Hispanic children with CKD have a 74% and 66% lower risk of fracture when compared to White children with pre-dialysis CKD [17]. Studies of racial differences in skeletal architecture and fracture risk have become less frequent in recent years. Still, questions remain

including which biological or genetic mechanisms underlie the differences in fracture risk and whether an understanding of these mechanisms can assist in the tailoring of ROD therapy to address the individual risk of ROD and fracture. It is critical to keep in mind that ROD exists beneath the umbrella of CKD-MBD which as an entity encompasses the important interaction between the skeleton, mineral and hormonal mediators, and the cardiovascular system. As such, a thorough approach to targeted ROD therapy must also consider the impact of treatment on the cardiovascular system.

The Implications of Racial-ethnic Differences in Biochemical Markers

Adding to the complexity of these racial-ethnic differences in bone histomorphometry is the inability to predictably attribute these differences to biochemical differences. One major complexity is the "skeletal paradox" whereby major biochemical markers including vitamin D and PTH tend toward less favorable levels (low vitamin D and elevated PTH) in Black individuals yet skeletal outcomes, including fracture, show a decreased risk. It is this paradox of less favorable markers yet stronger, less fracture-prone bone that places pressure on the current approach to treat all patients with CKD using universal target levels for surrogate markers of bone like PTH and vitamin D. Previous attempts to explain this paradox theorized that Black participants had similar bioavailable vitamin D for a given level of 25OHD due to lower levels of vitamin D binding protein (VDBP). In fact, previous studies *did* conclude that Black participants had lower VDBP levels resulting in similar bioavailable vitamin D [18]. It has become evident with time that previously described differences in VDBP were simply due to inadequate assays for VDBP detection. In fact, using the now validated measurement via mass spectrometry, we now know that, despite major differences in VDBP genotype by race, there are no racial differences in VDBP levels [19]. This new assay has helped to expand our knowledge of racial differences in calculated bioavailable vitamin D. A study by Hsu et al. comparing White and Black participants found that bioavailable vitamin D was strongly associated with both race and percent African ancestry. Within the Multi-ethnic Study of Atherosclerosis (MESA) population, Black participants had lower calculated bioavailable vitamin D than White participants and higher percent African ancestry was also associated with lower bioavailable vitamin D [20]. Similar to prior studies, Black participants had higher PTH but novel to this study was the finding of higher CYP27B1 activity and lower CYP24A1 activity both which may contribute to the maintenance of active, 1,25-dihydroxyvitmain D levels. Consistent with this, total 1,25-dihydroxyvitmain D levels were higher in Black participants than White participants but contrarily, bioavailable 1,25-dihydroxyvitmain D levels were lower. This suggests that the regulation of vitamin D may be more dynamic than is reflected by single measurements; reflections of enzymatic activity may give a better assessment of vitamin D homeostasis. The higher CYP27B1 activity, lower CYP24A1 activity in addition to lower urinary calcium excretion in Black participants within this study were thought to contribute to better calcium homeostasis which may potentially lead to better bone outcomes [21].

Implications to Clinical Practice: The Case for Moving Beyond Race

It is important to remember that race and ethnicity simply serve as an example of the heterogeneity inherent to ROD. Despite these differences being evident at a population level, ROD heterogeneity is inherent to the individual. Therefore, these racial-ethnic differences push us to discover bone biomarkers that are better predictors of ROD across various levels of clinical heterogeneity (race, ethnicity, disease etiology, age). Alternatively, the continued utility of PTH will rely upon an improved ability to predict the responsiveness of bone to a given PTH level across individuals. Currently, KDIGO-defined guidelines for PTH are broader than previously set standards and allow room for individual variation in the response of bone to PTH. Still, without iliac crest bone biopsy, it difficult to distinguish individuals who benefit from a PTH level that is on the lower end of the range from those who require a PTH closer to the upper limit of acceptable. At times, alkaline phosphatase may serve as an indicator of the response of bone to PTH. Assuming adequate phosphate and calcium levels, elevations in alkaline phosphatase may reflect elevated bone turnover allowing one to titrate, not only to PTH levels within 2–9 times the ULN, but also allowing for normalization of alkaline phosphatase

Table 1 Key Research questions to improve the understanding of Renal Osteodystrophy

Key Remaining Research Questions
• Which biomarker(s) alone, or in conjunction with PTH, reliably predicts bone turnover and mineralization, irrespective of race and ethnicity?
• What genetic, biological or environmental markers underly the heterogeneity of renal osteodystrophy?
• What constitutes vitamin D sufficiency across racial-ethnic groups but more specifically, across individuals
• How does a precision-approach to ROD, or lack thereof, impact cardiovascular outcomes?

to serve as an additional indicator of having achieved normal bone turnover. Although not currently measured routinely, bone specific alkaline phosphatase provides even greater discrimination than total alkaline phosphatase [21]. Unfortunately, alkaline phosphatase has limitations, particularly in children in whom mineralization defects are highly prevalent and contribute to alkaline phosphatase elevations.

In summary, racial-ethnic differences in bone serve as an indication of the need for greater knowledge about ROD and a need for validated biomarkers which better predict bone pathology across demographics and clinical categories. Although replicated by many research studies, current data on race and ethnicity is not yet at the stage to allow tailoring of treatment by race and ethnicity. But even more importantly, the goal for ROD is to achieve precision at the level of the patient. Given this, the factors that underly the associations we see by race and ethnicity are of true interest and greater study is required (Table 1).

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics This review has been conducted ethnically.

Competing Interests The authors declare no competing interests.

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• Of importance
•• Of major importance

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