Ethnic differences in bone and mineral metabolism in healthy people and patients with CKD

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Several studies have shown racial differences in the regulation of mineral metabolism, in the acquisition of bone mass and structure of individuals. In this review, we examine ethnic differences in bone and mineral metabolism in normal individuals and in patients with chronic kidney disease. Black individuals have lower urinary excretion and increased intestinal calcium absorption, reduced levels of 25(OH)D, and high levels of 1.25$(OH)_2$D and parathyroid hormone (PTH). Body phosphorus concentration is higher and the levels of FGF-23 are lower than in whites. Mineral density and bone architecture are better in black individuals. These differences translate into advantages for blacks who have stronger bones, less risk of fractures, and less cardiovascular calcification. In the United States of America, the prevalence of kidney disease is similar in different ethnic groups. However, black individuals progress more quickly to advanced stages of kidney disease than whites. This faster progression does not translate into increased mortality, higher in whites, especially in the first year of dialysis. Some ethnicity-related variations in mineral metabolism persist when individuals develop CKD. Therefore, black patients have lower serum calcium concentrations, less hyperphosphatemia, low levels of 25(OH)D, higher levels of PTH, and low levels of FGF-23 compared with white patients. Bone biopsy studies show that blacks have greater bone volume. The rate of fractures and cardiovascular diseases are also less frequent. Further studies are required to better understand the cellular and molecular bases of these racial differences in bone mineral metabolism and thus better treat patients.

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The risk of osteoporosis and fractures is different in various populations.[1] Individuals of African descent have higher bone density and fewer fractures than Caucasians, whereas Asians have lower fracture rates despite lower bone density. Ethnic variations are found in mineral metabolism, Ca homeostasis, serum concentrations of 25(OH)D and parathyroid hormone (PTH), as well as in acquisition of bone mass and structure.[2–10] These differences in bone metabolism may also be related to the differences seen in the frequency and severity of vascular calcifications (VCs).[11]

The analysis of US databases has revealed that although the prevalence of early stages of chronic kidney disease (CKD) is similar in different ethnic groups, black individuals progress to advanced stages of the disease four times faster than do Caucasians.[12] In a large health-care program, blacks had more extreme rates of renal function decline, and Asians progressed more slowly than the other groups.[13] However, once on dialysis, black patients have lower mortality rates.[14–17]

In this review, we examine ethnic differences in bone and mineral metabolism in normal individuals. As kidney disease progresses, patients develop CKD-MBD (mineral and bone disorder) that can be described by abnormalities in serum laboratory measures, bone disease, and VCs,[18] which all vary according to race.

ETHNIC DIFFERENCES IN LABORATORY MEASUREMENTS OF MINERAL METABOLISM IN HEALTHY INDIVIDUALS

The intake of Ca varies among different ethnic groups, some populations consuming between 300 and 400 mg/day, and others consuming three times these values.[19] Studies on calcium metabolic balance and kinetics have shown that African Americans ingest less Ca, have a more efficient intestinal absorption, and lower urinary excretion than whites.[6] Similar differences have also been observed between South African blacks and whites.[20]

Braun *et al.*[6] compared Ca intake and retention in white and black American adolescents and found that black teenagers retained more Ca in their skeleton (mean difference of 185 ± 32 mg Ca/day). For any amount of Ca intake, they excreted less Ca in the urine. Mechanisms involved in lower Ca urinary excretion in blacks are not yet fully known. In this study, the serum PTH and 25(OH)D

levels did not explain the urine calcium results.[6] Na *et al.*[21] demonstrated the existence of two black-specific variants in the gene encoding the renal epithelial channel TRPV 5 (A563T), a key protein in the regulation of renal tubular Ca handling. This variant, which is relatively common in blacks, might help to explain the lower urinary Ca excretion in these individuals. Another study evaluating Ca-sensing receptor polymorphism in blacks showed that the alleles associated with elevated blood pressure were associated with a decrease in urinary Ca excretion.[22]

Few studies have assessed ethnic differences in the metabolism of phosphate (Pi). Arunabh *et al.*[23] used delayed gamma neutron activation and studied total body Pi in 90 black females and 143 white females ranging in age from 20 to 70 years. Results showed that total body Pi was lower in whites (401 ± 58 vs. 448 ± 58 g) even after correction for body mass index. Total body Pi decreases with age, but the differences between black and white females remain over time.

Gutiérrez *et al.*[24] reported that blacks had a fractional excretion of Pi lower than that of whites, with similar serum PTH and fibroblast growth factor 23 (FGF23) serum levels. The results may have been altered by pre-treatment of black patients with high doses of vitamin D.

The serum concentration of 25(OH)D is consistently lower in blacks and hispanics than in whites, even after adjusting for age, gender, body mass index, intake of Ca, serum Ca and serum albumin.[25] This is related to greater skin pigmentation that inhibits cutaneous synthesis of cholecalciferol.[26] After an oral dose of vitamin D, blacks increase the serum levels to the same extent as whites.[27]

Serum concentrations of PTH and $1,25(OH)_2D$ are higher in blacks.[28] In a multi-ethnic study from the United States, Chinese subjects had lower PTH than white, black, or Hispanic subjects.[29] Serum 25(OH)D concentrations >20 ng/ml are not associated with further suppression of PTH in blacks, in contrast to what is observed in whites or Mexican-Americans.[25] In Japan, PTH levels are lower than in Western countries, and there was no correlation between PTH and 25(OH)D when the concentrations were >37 nmol/l.[30]

Fuleihan *et al.*[10] studied the sigmoidal Ca-PTH curve in the two ethnic groups and demonstrated that the maximum and minimum PTH response to hypocalcemia and hypercalcemia were higher in blacks, with no change in set point or slope of the curve. Autopsy findings revealed heavier parathyroid glands with higher cell numbers.[31] The higher serum levels of $1,25(OH)_2D$ in black people probably contribute to higher intestinal Ca absorption than in white people.[6]

In some studies, serum FGF23 concentrations do not appear to differ between normal black and white people[32,33] or between races in patients with coronary artery disease.[34] In the Cardiovascular Health Study, which included 497 normal black subjects >65 years, the FGF23 concentrations were lower in blacks than in whites.[35]

ETHNIC DIFFERENCES IN BONE MINERAL DENSITY AND FRACTURES IN HEALTHY INDIVIDUALS

Black persons have substantially lower fracture rates and higher bone density than individuals of other races. Asians have lower bone density than whites, but they also have lower fracture rates.[36–38] Hispanic people have also lower fracture rates than whites, with similar bone density.[25]

The increased bone density in blacks is already seen during childhood and adolescence. It is associated with better hip structural parameters and thicker cortices.[39] Femoral neck morphology differences between Chinese and white persons living in Australia are complex; the Chinese had a lower risk of fracture by buckling but a higher risk by bending.[40]

Although serum PTH levels are consistently higher in blacks, the bone formation rate is lower. They appear to have lower skeletal response to the PTH than whites. This was also demonstrated in a study by Cosman *et al.*,[41] who infused the biological active PTH fragment, PTH 1–34, and found that bone resorption markers showed lower responses in black subjects.

Ethnic differences in the relationship between serum 25(OH)D and fractures were reported from the Women's Health Initiative. In white women, those with 25(OH)D levels >20 ng/ml had fewer fractures (odds ratio 0.82), but the reverse was seen in black women, who had more fractures (odds ratio 1.45).[42] A similar trend was seen in older adults from the NHANES survey, where a standard deviation decrease in 25(OH)D concentration was associated with an odds ratio of 1.24 for fracture in whites but 0.81 in blacks.[43] Furthermore, a randomized clinical trial of vitamin D supplementation in black women found no improvement in fracture rates compared with placebo.[44]

Bone turnover markers (collagen-cross-links and osteocalcin) are lower in normal black men and women than in whites.[45,46] In a longitudinal study of perimenopausal women living in the United States, the increase in urine N-telopeptide was smaller in blacks and greater in Asians compared with whites.[47] Circulating sclerostin has been reported in one study of women aged >80 years, and it was lower in the blacks than in whites.[48]

Genome-wide analysis surveys have recently been conducted to search for possible relationship between genetic variation and bone density. These have found some significant polymorphisms that associate with bone density, but still there is no explanation for the racial differences.

ETHNIC DIFFERENCES IN BONE HISTOMORPHOMETRY FINDINGS AMONG HEALTHY SUBJECTS

Few studies have evaluated the histomorphometric parameters of bone tissue in normal individuals of different ethnicities. Some analyzed ethnic differences in the course of age,[49–51] others analyzed differences in the premenopause,[52] and others analyzed them in the premenopause and postmenopausal state.[53–56]

Schnitzler *et al.*[49] studied blacks and whites in South Africa ranging in age from 21 to 83 years. The results showed