Role of Vitamin D Receptor Activation in Racial Disparities in Kidney Disease Outcomes

Utibe Essien, MD, Narender Goel, MD, and Michal L. Melamed, MD, MHS

Summary: African Americans have lower 25-hydroxyvitamin D (25(OH)D) levels compared with whites. African Americans also have a higher risk of developing albuminuria and end-stage renal disease but a lower risk of death once they commence hemodialysis compared with whites. Vitamin D levels have been associated with multiple outcomes including albuminuria, progression to end-stage renal disease, and all-cause and cardiovascular mortality. In this review, we examine the evidence linking 25(OH)D to outcomes and the possibility that differential 25(OH)D may explain certain racial differences in outcomes.
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Much research has been performed on vitamin D and its supplementation over the past few years, particularly as related to patients with kidney disease. At the same time, racial disparities in chronic kidney disease and end-stage renal disease (ESRD), first described by Rostand et al,[1] continuously are being studied. Recently, a few studies have linked the two areas of study.[2–4] African-Americans, who make up 14% of our nation's population, account for one third of the 400,000 patients on dialysis.[5] Although African Americans have a higher risk of developing ESRD, they also have better survival rates than their white counterparts, at least at older ages.[6] This review discusses observational and clinical trial evidence regarding the effects of vitamin D and its analogs, both oral and intravenous, on all patients with kidney disease while specifically looking at the relationship between vitamin D and racial differences.

VITAMIN D PHYSIOLOGY

Vitamin D, discovered as an essential nutrient for the prevention of rickets, is key to the absorption of calcium and phosphorus in the body.[7] The vitamin can be obtained from foods such as oily fish, fortified milk, juices, breakfast cereals, and eggs.[7] Vitamin D also is obtained through the action of ultraviolet B radiation on the skin. When vitamin D enters the body, it is extracted by the liver and converted to 25-hydroxyvitamin D (25(OH)D). This form of vitamin D circulates in the bloodstream and is used to evaluate an individual's vitamin D status because of its long half-life. The more active form of vitamin D, 1,25-dihydroxyvitamin D, is created by the action of 1-α hydroxylase, an enzyme whose activity in the kidney is very much linked to body mineral levels. The 1-α hydroxylase enzyme also is found in other locations in the body.[7]

RACIAL DIFFERENCES IN VITAMIN D LEVELS

Racial differences in 25(OH)D levels have been described in many different populations (Table 1). The literature suggests that lower levels of serum 25(OH)D in African Americans and other individuals with dark complexions are caused by darker skin pigmentation, which decreases synthesis of vitamin D in the skin.[8–10] However, there are other potential factors that may influence these differences. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) showed that the use of multivitamins was associated with a lower prevalence of vitamin D deficiency.[11] Significantly fewer African Americans took multivitamins compared with whites.[11] African Americans also consumed fewer dairy products, which are sources of vitamin D, possibly because of lactose intolerance.[12] More leisure-time physical activity also has been associated with higher vitamin D levels, and African Americans in NHANES III participated in less leisure-time physical activity compared with whites.[13] A higher body mass index also has been shown to be associated with lower serum 25(OH)D levels.[14] In general, African Americans have a higher prevalence of obesity than whites,[15] and if vitamin D is sequestered in fat, explaining lower serum levels, then differential body mass indexes also may explain some of the racial differences in 25(OH)D levels. Thus, the reasons for racial differences in vitamin D levels are probably many and potentially are modifiable.

Departments of Medicine and Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY.
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Address reprint requests to Michal L. Melamed, MD, MHS, 1300 Morris Park Ave, Ullmann 615, Bronx, NY 10461. E-mail: michal.melamed@einstein.yu.edu
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Table 1. 25(OH)D Levels in Different Race/Ethnicities in Different Studies

Study	Whites mean (ng/mL)	White, % <15 ng/mL	Black mean, (ng/mL)	Black, % <15 ng/mL	Hispanic mean (ng/mL)	Hispanic, % <15 ng/mL
NHANES III[2,97]	Men, 33.3; women, 30.4	5	Men, 20.9; women, 18.1	35	Men, 27.4; women, 22.7	13
NHANES 1999-2004[77]	24.8	3	15.5	11	21.5	29
AusDiabetes[53]	26.1	N/A	18.9	N/A	N/A	N/A
ArMORR[75]	23.2	15	16.9	30	20.7	13
Cardiovascular health study[98]	N/A	21.0	N/A	47	N/A	21.9
HOST[93]	21	28.0	14	59.9	N/A	N/A

Abbreviations: ArMORR, accelerated mortality in renal replacement; HOST, Homocysteinemia in Kidney and End Stage Renal Disease Study.

CHRONIC KIDNEY DISEASE: MINERAL AND BONE DISORDERS

As kidney function worsens, there is decreased activity of 1-α hydroxylase, and decreased 1,25-dihydroxyvitamin D levels develop. These low levels result in low calcium levels and high parathyroid hormone (PTH) levels, or secondary hyperparathyroidism, a common finding in patients with chronic kidney disease. At the same time, as kidney function declines, the kidney becomes less efficient in excreting excess phosphate. Fibroblast growth factor 23 (FGF-23) is a recently discovered phosphaturic hormone secreted by bone that increases as kidney function worsens.[16,17] FGF-23 levels increase early in chronic kidney disease (CKD), probably in response to phosphate loads.[18] Increased PTH levels are associated with renal osteodystrophy, but more importantly are associated with poor outcomes in dialysis patients, including mortality.[19] Increased FGF-23 levels also are associated with a higher risk of morbidity and mortality in kidney disease.[20–22] The mortality in these patients appears especially related to cardiovascular disease, which is the most common cause of death among dialysis patients.[23] Nevertheless, the lack of clinical trials showing that normalization of chronic kidney disease/mineral bone disorder parameters decrease mortality will allow the controversy regarding management of patients with ESRD to continue.

Multiple studies have found that African Americans have higher PTH levels and lower 25(OH)D levels compared with whites, both in patients with kidney disease and in the general population.[2,4,24] In NHANES III, 34% of non-Hispanic black individuals had 25(OH)D levels less than 15 ng/mL compared with 5% of non-Hispanic white individuals ($P < .001$).[2] Interestingly, racial differences in serum phosphorus and alkaline phosphatase levels are not commonly described. In a study by Kalantar-Zadeh et al,[25] although black patients on hemodialysis treated with vitamin D had consistently higher serum PTH levels, serum phosphorus and alkaline phosphatase levels did not differ from non-black patients.

In this review of other possible outcomes associated with low 25(OH)D levels, it is important to remember that currently the use of vitamin D in patients with kidney disease is approved for control of secondary hyperparathyroidism. Two Cochrane reviews[26,27] showed that in both dialysis and predialysis CKD patients, calcitriol and vitamin D analogs decreased PTH (−196 pg/mL; 95% confidence interval, −298 to −94 in dialysis patients; −49 pg/mL, 95% confidence interval, −86 to −13 in predialysis patients), but increased serum phosphate and calcium levels. Not enough data exist from randomized clinical trials to make conclusions about patient outcomes such as fractures, mortality, or need for dialysis in predialysis patients.[26,27] Another meta-analysis of nutritional vitamin D compounds recently was performed and found that in 4 randomized clinical trials including both dialysis and nondialysis CKD patients, PTH levels decreased significantly by −31.5 pg/mL (95% confidence interval, −57 to −6.1).[28] There was no evidence regarding patient outcomes.[28]

RACE, GENETICS, AND CKD

The causes of health disparities are many and complex and are not reviewed completely in this article.[29] In this section, we discuss other potential causes of racial disparities in kidney disease, some of which are examined in more detail in other articles in this issue of *Seminars in Nephrology*. Some causes include socioeconomic factors such as access to care, quality of care differences among underserved patient populations, barriers to patient-physician communication, and a higher prevalence of some of the earlier-mentioned comorbidities in minority populations (Table 2). Many of the earlier-described factors are modifiable, however, there are some that are nonmodifiable, including genetic factors. Studies have shown that non-Hispanic