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

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Abstract

African-Americans have lower 25-hydroxyvitamin D (25(OH)D) levels compared to 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 to 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.

Introduction

Much research has been done on Vitamin D and its supplementation over the last 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 Rostand¹ and others are continuously 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 While African-Americans have a higher risk of developing ESRD, they also have better survival than their white counterparts, at least at older ages.⁶ This review will discuss 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.

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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 is also 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-alpha hydroxylase, an enzyme whose activity in the kidney is very much linked to body mineral levels. The 1-alpha hydroxylase enzyme is also 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 due to 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 to whites.¹¹ African-Americans also consumed fewer dairy products, sources of vitamin D, possibly due to lactose intolerance.¹² More leisure-time physical activity has also been associated with higher vitamin D levels and African-Americans in NHANES III participated in less leisure-time physical activity compared to whites.¹³ A higher BMI has also been shown to be associated with lower serum 25(OH)D levels.¹⁴ In general, African-Americans have a higher prevalence of obesity than whites¹⁵ and if vitamin D is sequestered in fat explaining lower serum levels, then differential BMIs may also 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 modifiable.

Chronic Kidney Disease - Mineral and Bone Disorders

As kidney function worsens, there is decreased activity of 1-alpha hydroxylase, and decreased 1,25-dihydroxyvitamin D levels develop. These low levels result in low calcium levels and high 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 CKD probably in response to phosphate loads.¹⁸ Elevated parathyroid hormone levels are associated with renal osteodystrophy but more importantly with poor outcomes in dialysis patients, including mortality.¹⁹ Elevated FGF-23 levels are also 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 decreases mortality will allow the controversy over 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 to 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 <15 ng/ml compared with 5% of non-Hispanic white individuals ($P < 0.001$).² Interestingly, racial differences in serum phosphorus and alkaline phosphatase levels are not commonly described. In a study by Kalantar-Zadeh et al., 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.²⁵

In this review of possible other 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 pre-dialysis CKD patients, calcitriol and vitamin D analogs decrease PTH (-196 pg/ml, 95% CI: -298 to -94 in dialysis patients; -49 pg/ml, 95% CI: -86 to -13 in pre-dialysis patients) but increase 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 pre-dialysis patients.^{26,27} Another meta-analysis of nutritional vitamin D compounds was recently performed and found that in 4 randomized clinical trials including both dialysis and non-dialysis CKD patients, PTH levels decreased significantly, -31.5 pg/ml (95% CI: -57 to -6.1).²⁸ There was no evidence regarding patient outcomes.²⁸

Race, Genetics, and Chronic Kidney Disease

The causes of health disparities are many and complex and will not be 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 amongst underserved patient populations, barriers to patient-physician communication and higher prevalence of some of the above-mentioned co-morbidities in minority populations (Table 2). Many of the above factors are modifiable, however, there are some that are non-modifiable, including genetic factors. Studies show that non-Hispanic blacks have a similar prevalence of stage 1 through 4 chronic kidney disease as whites but have a higher incidence of ESRD.^{30,31} This suggests that either non-Hispanic blacks progress faster through the stages of CKD or that white individuals die of other causes than ESRD. Potential explanations for the racial difference in ESRD incidence are the low nephron hypothesis, which states that from birth, humans with lower nephron numbers are more likely to develop proteinuria, high BP and other renal disease.³² African-Americans have lower birth weights and therefore may have lower nephron mass. The identification of associations between apolipoprotein L1 gene variants and prevalent kidney disease and kidney disease progression may explain much of the increased risk of non-diabetic kidney disease in African-Americans.^{33,34} The variant gene is protective against African sleeping sickness, caused by *Trypanosoma brucei*, which potentially explains its

higher prevalence in African-Americans.³⁵ The association between the APOL-1 gene variant and kidney disease has been found in many types of kidney diseases including focal and segmental glomerulosclerosis and HIV nephropathy, as discussed in more detail in another paper in this issue.³⁶

Race, Vitamin D, UV Light and Blood Pressure Differences

Hypertension is a common finding in patients with kidney disease, is more common in African-Americans³⁷ and is associated with low 25(OH)D levels. In the 1990s, Rostand hypothesized that as vitamin D photosynthesis decreases with high skin melanin and decreased UV light intensity, vascular smooth muscle growth is stimulated which in turn leads to increased contractility due to the effects on intracellular calcium and endothelial function.³⁸ These changes thus may contribute to the racial differences in blood pressure and hypertension.³⁸ Several recent studies show an association between low vitamin D levels and high blood pressure in humans. Low 1,25(OH)2D levels have an inverse association with plasma renin activity.³⁹ A study in 184 normotensive individuals on a high sodium diet, showed that participants with 25(OH)D deficiency (<15 ng/mL) had higher circulating angiotensin II, a hormone downstream from renin.⁴⁰ Epidemiologic studies show an association between low 25(OH)D levels and incident hypertension.⁴¹ Several clinical trials have evaluated the effects of vitamin D supplementation on blood pressure. Some small studies have shown a decrease in blood pressure with vitamin D treatment (sample sizes=20,⁴² 148,⁴³ and 34⁴⁴). The effect sizes included a 9.3% decrease in systolic blood pressure⁴³ and a 14 mmHg⁴⁴ decrease in systolic blood pressure at fairly high doses of vitamin D, approximately 800-1600 IU/day. Not all trials have shown similar changes in blood pressure.⁴⁵ An analysis of NHANES 2001-2006 data revealed that about a quarter of the difference in blood pressure between non-Hispanic blacks and whites can be explained by differences in 25(OH)D levels.⁴⁶

Vitamin D and Chronic Kidney Disease

There are many ways to measure dysfunction of the kidneys. Two of the most common ways are the presence of albumin in the urine (albuminuria) and decreased glomerular filtration rate (GFR) which eventually leads to the need for renal replacement therapy. Many different factors lead to the development of end-stage renal disease (Figure). Mouse models have shown that vitamin D suppresses renin.⁴⁷ Other animal models have shown effects of vitamin D and its analogs on decreasing proteinuria.⁴⁸ Still other studies have observed that active vitamin D decreases albuminuria in multiple animal models of kidney disease.⁴⁹⁻⁵¹ Rats who are treated with 1,25-dihydroxyvitamin D₃ had less albuminuria and showed preserved slit diaphragm protein morphology.⁴⁸ Rats treated with vitamin D analogs also had lower levels of TGF-1 protein in the tubules and glomeruli compared to nontreated rats, a cytokine that regulates cellular proliferation and extracellular matrix deposition.⁵¹

In humans, observational data shows that low levels of 25(OH)D are associated with a higher prevalence and risk of development of albuminuria. In both the NHANES III and the Australian Diabetes, Obesity and Lifestyle studies low levels of 25(OH)D are associated with a higher prevalence of albuminuria.^{52,53} In a long-term follow-up of the Diabetes Control and Complications Trial, participants with low 25(OH)D levels (<20 ng/mL) at

baseline followed over 16 years were more likely to develop microalbuminuria compared to participants with high 25(OH)D levels.⁵⁴ Albuminuria is more common in African-Americans than in whites (10% vs. 6.6% in NHANES 2001-2006).⁵⁵ In this latter study, when the authors adjusted for 25(OH)D levels the racial difference in albuminuria became not statistically significant.⁵⁵

Several studies have shown that activated vitamin D therapy can decrease albuminuria.⁵⁶⁻⁵⁸ A large, placebo-controlled, double-blinded, randomized clinical trial (the VITAL study) by de Zeeuw *et al.* evaluated two different doses of paricalcitol as compared to placebo in 281 participants with type 2 diabetes mellitus.⁵⁶ This study showed lower urine protein/creatinine ratios, lower rates of albumin excretion and lower PTH levels in patients randomized to 2 micrograms of paricalcitol compared to those on placebo. Patients in the higher paricalcitol dose also experienced substantially reduced estimated GFR after just 4 weeks of treatment as measured by serum creatinine. It is unclear if this change in serum creatinine is actually a change in kidney function.⁵⁹ While the study showed improvement in albuminuria, it is unclear whether this will translate to improved clinical outcomes.

While the evidence for effects of activated vitamin D on albuminuria are fairly convincing, the association of vitamin D and estimated GFR and kidney disease progression is not as robust. In 1705 older adults in the Cardiovascular Health Study (CHS) with mean age 74 years, low 25(OH)D levels were associated with a more rapid eGFR loss and with a combined endpoint of rapid GFR loss, ESRD or death.⁶⁰ In patients with kidney disease, low 25(OH)D levels were associated with earlier initiation of renal replacement therapy and death.⁶¹ An analysis of NHANES III data showed participants with 25(OH)D levels <15 ng/ml had a 2.6-fold greater incidence of ESRD than those with levels >15 ng/ml.² This study went on to evaluate whether low 25(OH)D levels may be responsible for some of the increased risk of ESRD in African-Americans compared to whites. It found that vitamin D deficiency was responsible for up to 58% of the increased risk of ESRD in African Americans as compared to non-Hispanic whites.² In summary, observational data reveals low 25(OH)D levels are associated with loss of GFR and may be responsible for some of the racial differences in kidney disease progression.

Hispanics, Vitamin D and Chronic Kidney Disease

Although most previous studies of racial disparities in ESRD have focused on non-Hispanic black and non-Hispanic white individuals, it is important to note that Hispanic individuals also have a higher risk for ESRD and have lower vitamin D levels than white individuals.² The nephrology research community needs to focus attention on racial/ethnic differences in the Hispanic community as well.

Vitamin D and Cardiovascular Disease

Patients with CKD suffer from a higher risk of cardiovascular mortality than individuals in the general population and frequently have left ventricular hypertrophy (LVH) and diffuse vascular calcification. Beyond classic risk factors, researchers have explored other risk factors such as inflammation, oxidative stress, and chronic kidney disease- mineral bone disorder including derangements in vitamin D and FGF-23 levels. An association between

low vitamin D levels and LVH is clear in animal models but not as clear given recent data in humans. The vitamin D receptor knock-out mouse develops LVH and 1,25-dihydroxyvitamin D has been shown to regulate myocyte proliferation by blocking their entry in to S-phase of cell cycle.^{62,63} High FGF-23 levels also cause LVH in animal models.⁶⁴ In humans, treatment with paricalcitol for 48 weeks in patients with CKD did not change left ventricular myocardial index as shown by recent study by Thadhani *et al.*⁶⁵ In a post hoc analysis, paricalcitol treatment did decrease left atrial volume index⁶⁶ in this same study. It is unclear at this point why paricalcitol did not decrease LVH in the PRIMO trial as it did in animal models.⁶⁷ It may be that in humans, LVH is not the correct parameter to evaluate, that paricalcitol caused higher FGF-23 levels leading to LVH through a different mechanism, or other possible explanations.

Interestingly, vitamin D levels have been associated with both more and less vascular calcification. A study by Freedman *et al.* showed positive association between vitamin D levels and aorta and carotid artery calcified plaques, markers of subclinical atherosclerosis but not with coronary artery plaques in African-Americans.⁶⁸ Another study, where the race of the participants was not specified, showed that 1,25-dihydroxyvitamin D level inversely correlated with coronary calcification.⁶⁹ There is some recent evidence suggesting that vitamin D receptor activators decrease aortic calcification in mice by increasing serum klotho and up regulating vascular smooth muscle cell osteopontin independently of serum calcium and PTH level.⁷⁰

Low levels of 25(OH)D and 1,25-dihydroxyvitamin D have been associated with increased cardiovascular mortality in the general population⁷¹⁻⁷³ and in patients with ESRD.^{74,75} In the general population, African-Americans have a higher risk of cardiovascular mortality and peripheral arterial disease.^{76,77} Interestingly, similar analyses of NHANES data showed that after accounting for 25(OH)D levels some of the disparity in these outcomes is attenuated.^{77,78} An analysis of stroke deaths using NHANES III data revealed a higher risk of stroke with low 25(OH)D levels in white participants but not in black participants, suggesting that there may be racial differences in 25(OH)D associations with outcomes.⁷⁹ Despite these studies and a number of observational studies revealing an association between low 25(OH)D levels in patients with CKD and ESRD and a higher risk of all-cause mortality,⁷⁵ there are still few published reports of associations between nutritional vitamin D supplementation and improved survival in kidney disease while the data on the general population is mixed.^{80,81}

Race, Vitamin D and Dialysis Survival

Although black individuals have some of the worst health outcomes in the country, when it comes to individuals on hemodialysis, older blacks have the best survival.⁶ Newsome *et al.*, looking at data from acute myocardial infarction patients in the Cooperative Cardiovascular Project, showed there may be a survival advantage for black individuals with chronic kidney disease even before they develop ESRD.⁸² In an attempt to understand the finding of racial differences in survival on dialysis—in particular the fact that over the past twenty years, blacks receiving maintenance hemodialysis have an annual death rate of only 187 per 1000 patient years versus 207 per 1000 patient years in non-Hispanic whites receiving

maintenance hemodialysis⁸³— Kalantar-Zadeh *et al.* studied over 100,000 patients who were being treated thrice-weekly in hemodialysis, including 32% blacks. The study found that blacks had higher serum calcium and parathyroid hormone levels and were more likely to receive active injectable vitamin D and at higher doses than non-blacks.²⁵ Blacks in the study who received the highest dose of paricalcitol experienced a survival advantage over those who received lower doses or no active vitamin D at all.²⁵

Wolf et al. also observed in a study of incident hemodialysis patients that treatment with active vitamin D agents may be a potential explanation for better survival of African-Americans on dialysis.⁴ Again, it was noted that African-American patients were more likely to have higher parathyroid hormone levels and thus more likely to receive activated vitamin D and at higher dosages.⁴ Of the patients treated with activated vitamin D, black patients had 16% lower mortality compared with white patients, but the difference was lost when adjusted for vitamin D dosage.⁴ In contrast, untreated black patients had 35% higher mortality compared with untreated white patients. Of note, the black patients in the untreated group had significantly higher risk for mortality based on co-morbidities as compared to their white counterparts, which may attribute to their higher mortality.⁴ Thus, these two studies suggest that potentially part of the explanation for better survival of African-American patients on dialysis may be the fact that they are more likely to be exposed to vitamin D therapy. No randomized clinical trials have tested this hypothesis.

Ideal Vitamin D Levels? A Note of Caution

Experts disagree on the ideal 25(OH)D level for adults. Some suggest that 25(OH)D levels of 21 to 30 ng/ml indicate vitamin D insufficiency and levels 20 indicate vitamin D deficiency, levels associated with maximum PTH suppression.⁷ Others believe >20 ng/mL is adequate for most individuals.⁸⁴ It is interesting to note that much of the data regarding ideal 25(OH)D levels came from studies evaluating the PTH/ 25(OH)D relationship. Gutierrez *et al.*, in studying 8,415 participants in NHANES 2003-2006 observed that blacks and Mexican-Americans had significantly lower 25(OH)D levels, higher PTH concentrations and less calcium intake as compared to whites.⁸⁵ However, while an inverse relationship was observed between 25(OH)D and PTH in whites and Mexican-Americans above and below a level of 20ng/ml, this inverse association was only noted below the threshold in blacks.⁸⁵ Similar findings have been found in studies with smaller groups of participants.⁸⁶ This suggests that race-specific ranges of optimal vitamin D therapy may be appropriate.

Several other studies suggest that race-specific optimal vitamin D ranges may be appropriate. This includes the above mentioned study which showed a direct cross-sectional correlation between 25(OH)D levels and vascular calcification in African-Americans.⁶⁸ Black individuals maintain higher bone mineral density (BMD) than white individuals and have lower skeletal fractures despite lower 25(OH)D levels and higher PTH concentrations.^{87,88} An analysis of the Women's Health Initiative observational study revealed that African-Americans have a higher risk of a clinical fracture at high (>20 ng/mL) whereas similar 25(OH)D levels were associated with a lower risk of clinical fracture in white women.⁸⁹ Aloia et al looked at the change in postmenopausal African American women who were assigned to receive either vitamin D₃ supplementation or

placebo and found no significant difference in BMD change between the two groups.⁹⁰ These studies suggest that higher levels of 25(OH)D (>30 ng/mL) may not be protective against bone loss in African-Americans and may even be harmful (vascular calcifications).

While we don't completely understand the difference in the 25(OH)D relationship with outcomes in different races, there are some studies that may suggest mechanisms underlying these differences. Several studies have looked at bioavailable vitamin D, which is the fraction of circulating 25(OH)D that is not bound to either vitamin D binding protein or albumin and is thus available to produce biologic actions.⁹¹ Bioavailable 25(OH)D is higher in African-Americans compared to whites and is strongly correlated with bone mineral density and serum PTH and calcium levels.^{91,92} This may explain the paradox of why African-Americans have lower 25(OH)D levels but higher BMD—namely, they have more bioavailable 25(OH)D. Another possible explanation may be differential FGF-23 levels. FGF-23 levels have been shown to be lower in African-American and Hispanic patients with kidney disease along with lower 25(OH)D but higher 1,25-dihydroxyvitamin D levels as compared to whites.^{22,93} Physiologically, if African-Americans have lower FGF-23 levels compared to whites and lower 25(OH)D levels, they should be better able to convert 25(OH)D to 1,25-dihydroxyvitamin D because FGF-23 inhibits this conversion, thus allowing for higher levels of the more active hormone. Another hypothesis is that African-Americans are more efficient than whites in absorbing calcium intake and thus may require less dietary calcium than whites to maintain bone health and in turn less vitamin D.^{94,95}

Current Recommendations and On-going Studies of Vitamin D

There are several current ongoing studies of vitamin D supplementation. One hundred and five dialysis patients, as part of the Dialysis Infection and Vitamin D in New England (DIVINE) study, are being randomized to high-dose ergocalciferol, low dose ergocalciferol or placebo for 12 weeks (NCT 00892099). Primary end points include PTH levels and incidence of infection. Another study is currently evaluating the effect of ergocalciferol supplementation versus placebo on albuminuria and 24 hour blood pressures in patients with CKD stage 3 and 4 (NCT 01029002). Additional studies are needed in diverse patient populations to allow for conclusions within different racial/ ethnic sub-groups. Current opinion-based recommendations suggest measuring 25(OH)D levels and repletion using doses used in the general population (Table 3).⁹⁶

Summary/ Conclusions

African-Americans have lower levels of 25(OH)D and worse health outcomes compared to whites. These include a higher risk of hypertension, diabetes mellitus, stroke, end-stage renal disease and cardiovascular disease and mortality in the general population. Many of the poor health outcomes experienced by African-Americans are also associated with low 25(OH)D levels. Interestingly, some African-Americans on dialysis experience better survival on dialysis and receive more activated vitamin D than white patients. African-Americans also have higher bone mineral density compared to whites in spite of lower 25(OH)D levels. Whether differences in vitamin D levels or vitamin D metabolism between African-Americans and whites explain these paradoxes and differences in health outcomes still needs to be proven. While some hypotheses about these differences including

differential bioavailability, differential FGF-23 levels and others have been brought forth in recent years, definitive studies still need to be done. Large randomized clinical trials with adequate numbers of whites and African-Americans need to be conducted to be able to answer these important questions.

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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: NHANES: National Health and Nutrition Examination Survey; ArMORR: Accelerated Mortality in Renal Replacement; HOST: Homocysteinemia in Kidney and End Stage Renal Disease Study

Table 2

Racial disparities in selected health outcomes.

Disease/Condition	Denominator (persons)	White	African American	Mexican American
Incident ESRD ⁵	Per million	276	924	501
Hypertension ³⁷	Per 100	Male: 29.8 Female: 26.9	Male: 39.6 Female: 43.1	Male: 26.3 Female: 27.7
Diabetes Mellitus ⁹⁹	Per 100	Male: 5.6 Female: 6.1	Male: 8.2 Female: 11.4	Male: 5.4 Female: 7.8
Obesity ¹⁰⁰	Per 100	34.9	49.6	39.6
Peripheral Arterial Disease ⁷⁷	Per 100	5.3	8.5	N/A
Cardiovascular mortality ⁷⁶	Per 10,000	11.5	25.1	N/A

Abbreviations: ESRD – end-stage renal disease, CKD – chronic kidney disease, CVD – cardiovascular disease

Table 3

Current Kidney Disease Improving Global Outcomes (KDIGO) related to vitamin D use in kidney disease.⁹⁶

Levels of Evidence	Recommendation
2C ^{**}	In patients with CKD stages 3-5D, we suggest that calcidiol (25(OH)D) might be measured, with repeated testing determined by baseline values and therapeutic interventions
2C	In CKD stages 3-5 not on dialysis therapy, suggest evaluating patients with PTH levels above the upper reference limit of the assay for hyperphosphatemia, hypocalcemia and vitamin D deficiency
2C	Suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population*
2C	Suggest that vitamin D deficiency and insufficiency be corrected in transplant patients
	* Possible recommended repletion doses: Cholecalciferol 1000-2000 international units/ day or ergocalciferol 50,000 international units per week for 8-12 weeks. Recheck calcium, phosphate, vitamin D and PTH after treatment to guide therapy.

^{**} 2C recommendations: strength of the recommendation: 2: weak or discretionary; evidence upon which it is based: C: low