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### The Low Blood Level of 25-Hydroxy Vitamin D in African American Women: Is It Clinically Significant?

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#### Abstract

After vitamin D (also called cholecalciferol) is synthesized in the skin, it is metabolized to 25(OH)D (25-hydroxyvitamin D, also called calcidiol) in the liver and then to the biologically active form, 1,25(OH)<sub>2</sub>D (1,25-dihydroxyvitaminD, also called calcitriol) in the kidney. According to the guidelines of the Endocrine Society, vitamin D deficiency is defined as a blood level of 25(OH)D of 20 ng/ml or lower, and with this definition an estimated 42% to 82% of African Americans are considered vitamin D deficient. However, there is no concrete evidence of higher-than-normal rates of common disorders of vitamin D deficiency within the African American population. Our review of independent studies clearly shows that although the mean blood levels of 25(OH)D in African American women are in the deficient range, the mean blood levels of 1,25(OH)<sub>2</sub>D in African American women are unequivocally in the normal range and that African American women of different age groups also maintain normocalcemia (normal blood calcium level). Furthermore, although oral supplementation of high doses of vitamin D to African American women increases their blood levels of 25(OH)D to the normal range, there is no health benefits of the supplementation when bone health is concerned. Therefore, it appears that African American women are functionally vitamin D sufficient given that they have normal blood levels of 1,25(OH)<sub>2</sub>D, and the blood 25(OH)D level may not be the best marker of vitamin D sufficiency or deficiency in African American women. In the future, it will be critical to investigate if there are specific genetic factors that enable African American women to maintain normal blood levels of 1,25(OH)<sub>2</sub>D and bone health despite having low blood levels of 25(OH)D.

**Keywords:** African American; Women; Vitamin D; Deficiency; Health

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The established biological function of vitamin D is to regulate the homeostasis of calcium and phosphate for the maintenance of bone health. The importance of vitamin D for bone health is underscored by the fact that rickets in children and osteomalacia in adults result from prolonged vitamin D deficiencies or metabolic defects that impair the production of 1,25(OH)<sub>2</sub>D, or defects in the vitamin D signal transduction pathway [1-3]. Additionally, many studies have found an association between vitamin D deficiency and increased incidence of a plethora of chronic diseases, including cancers, autoimmune diseases, infectious diseases, cardiovascular diseases, and diabetes [1-3]. However, the causative role of vitamin D deficiency in many non-skeletal diseases remains uncertain or may not exist [4]. For example, although the blood levels of 25(OH)D were reported to be inversely correlated to the risk of colorectal cancer [5,6], the latest results of a well-designed study involving 2259 subjects demonstrate that daily supplementation of a high oral dose of vitamin D (1000 IU) plus or minus calcium (1200 mg) over a period of 3-5 years does not have any significant inhibitory effect on the development of colorectal carcinomas [7].

The simplified schemes in Figure 1 depict the synthesis and metabolism of vitamin D and regulations of vitamin D metabolism. Irradiation of the human skin by UV-B light causes non-enzymatic conversion of 7-dehydrocholesterol to pre-vitamin D<sub>3</sub> in the epidermis. Pre-vitamin D<sub>3</sub> then undergoes a spontaneous isomerization to vitamin D<sub>3</sub>, which is secreted into the blood circulation. Vitamin D<sub>3</sub> is absorbed from the blood circulation by the liver and then converted to 25(OH)D<sub>3</sub> through a reaction catalyzed by the enzyme CYP2R1 (also called vitamin D 25-hydroxylase). The 25(OH)D<sub>3</sub> is secreted back into the blood circulation. In the blood circulation, the vitamin D-binding protein (VDBP), which is also called group-specific component (Gc) protein encoded by the GC gene [8], serves as the carrier of 25(OH)D<sub>3</sub>. In response to decreasing concentration of blood Ca<sup>2+</sup>, the parathyroid glands secrete the parathyroid hormone (PTH), which stimulates bone resorption to release calcium and phosphate and causes inhibition of urinary excretion of calcium and increases urinary excretion of phosphate. As a long-term action mechanism, PTH stimulates the activation of CYP27B1 (also called 1-α-hydroxylase) in the renal proximal convoluted tubule, thereby causing increased conversion of 25(OH)D<sub>3</sub> to the biologically active 1,25(OH)<sub>2</sub>D<sub>3</sub> in the kidney and increased concentration of 1,25(OH)<sub>2</sub>D in the blood circulation. It should be noted that 1,25(OH)<sub>2</sub>D<sub>3</sub> molecules in the circulating blood are also bound to VDBP [8]. 1,25(OH)<sub>2</sub>D<sub>3</sub> enters a target cell, binds to the vitamin D receptor (VDR) in the nucleus, and activates the transcription activity of the receptor to induce changes in the expression of a large number of vitamin D-responsive genes [2]. In the small intestine, 1,25(OH)<sub>2</sub>D<sub>3</sub> regulates the expression of a set of genes to stimulate increased intestinal absorption of both calcium and phosphate [9]. In the kidney, 1,25(OH)<sub>2</sub>D<sub>3</sub> stimulates re-absorption of calcium [9,10]. Therefore, 1,25(OH)<sub>2</sub>D is an critical regulator of the calcium homeostasis of the blood. Thus, deficiency of 1,25(OH)<sub>2</sub>D<sub>3</sub> and defects in the vitamin D signaling pathway result in poor bone mineralization causing bone softening and rickets in children and osteomalacia in adults. Also, it should be noted that 1,25(OH)<sub>2</sub>D<sub>3</sub> inhibits PTH secretion by the parathyroid glands to prevent excessive bone resorption and 1,25(OH)<sub>2</sub>D<sub>3</sub> has a feedback inhibitory effect on the expression of CYP27B1, indicating self-regulation [9-11]. It should be noted that FGF23, which is secreted by osteoblasts and osteocytes in response to increasing circulating level of phosphate and which plays a critical role in phosphate homeostasis, also regulates vitamin D metabolism: FGF23 inhibits the metabolic conversion of 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub> by suppressing the expression of CYP27B1 and activating the expression of CYP24A1 (also called 24-α-hydroxylase), which is the key enzyme for catabolic degradation of vitamin D [12, 13] (Figure 1).

In addition to the UV-B light-stimulated synthesis of vitamin D<sub>3</sub> in the skin, humans obtain vitamin D, in the form of vitamin D<sub>2</sub> (a plant-produced vitamin D, also called ergocalciferol) or vitamin D<sub>3</sub>, from foods and/or vitamin D supplements. The dietary vitamin D<sub>2</sub>, after being absorbed into the human body, undergoes the CYP2R1- and CYP27B1-mediated metabolic changes to become the biological active 1,25(OH)<sub>2</sub>D<sub>2</sub> (for convenience, vitamin D<sub>2</sub> and vitamin D<sub>3</sub> will be referred to as vitamin D henceforth). Since the UV-B light-stimulated cutaneous synthesis of vitamin D<sub>3</sub> is most likely to contribute more than 90% of the vitamin D needed by the human body [3], and given that melanin is an excellent natural absorbent of the UVB photon, it is not surprising that dark-skinned people require substantially more exposure to UVB light than fair skinned people in order to synthesize an adequate amount of vitamin D per unit of skin area [14, 15]. Consequently, African Americans are more susceptible than Caucasians to developing vitamin D deficiency in the absence of adequate sunlight exposure or without taking vitamin D supplements [14, 15].

Despite the fact that 1,25(OH)<sub>2</sub>D is the biologically active form of vitamin D, the determination of the vitamin D status in the human body is made by measuring the total blood level of 25(OH)D. According to the guidelines of the Endocrine Society published in 2011 [16], vitamin D deficiency is defined as a blood 25(OH)D<sub>3</sub> level of 20 ng/mL or lower; vitamin D insufficiency is defined as a blood 25(OH)D<sub>3</sub> level of 21-29 ng/mL; and vitamin D sufficiency is defined as blood 25(OH)D<sub>3</sub> levels of 30 ng/mL or higher. However, Bischoff-Ferrari suggested that blood 25(OH)D<sub>3</sub> levels of 36-40 ng/mL are optimal after careful analysis of the thresholds of blood 25(OH)D<sub>3</sub> levels and its

relationship to skeletal health, dental health, risk of falls, fractures, and colorectal cancer [17].

According to the definition of vitamin D deficiency by the Endocrine Society guidelines, it is estimated that 42% to 82% of African Americans appear to be vitamin D deficient [18,19] in comparison to a less than 5% vitamin D deficiency incidence in the Caucasians [18]. However, there is no strong evidence of higher incidence of bone-related complications and symptomology of vitamin D deficiency in the African American population. Instead, African Americans of both genders actually have higher bone mass density, higher bone strength and less risk of bone fracture than Caucasians [20-25]. For example, postmenopausal Caucasian women are two to three times more likely than postmenopausal African American women to have non-vertebral fracture [24,25]. Therefore, the blood level of 25(OH)D does not seem to serve as a reliable biomarker for bone health of the African Americans. To seek an explanation for this apparent discrepancy of vitamin D deficiency versus a lack of increased risk of bone disorders in African Americans, we reviewed published studies that have specifically compared blood levels of vitamin D, calcium, and parathyroid hormone and other factors between African American women and Caucasian women. We also reviewed studies that investigated potential health benefits of high oral doses of vitamin D supplementation to African American women. The findings of these studies show that compared to Caucasian women African American women of all age groups have a high incidence of vitamin D deficiency according to the blood 25(OH)D levels. However, African American women maintain normal blood levels of the biologically active 1,25(OH)<sub>2</sub>D, making them functionally vitamin D sufficient, and furthermore even though high oral doses of vitamin D supplementation increase the blood level of 25(OH)D in African American women it does not seem to have any significant effect on the bone health of the African American women.

## Findings

### Blood levels of 25(OH)D, 1,25(OH)<sub>2</sub>D, Ca<sup>2+</sup>, and PTH in African American women versus Caucasian women

In comparison to age-matched Caucasian women, the mean blood levels of 25(OH)D in African American women at all life stages - from peripubertal to postmenopausal ages—are in the deficient range (Table 1). However, when the blood 1, 25(OH)<sub>2</sub>D levels between age-matched African American and Caucasians women are compared, the mean blood and 1, 25(OH)<sub>2</sub>D levels of African American women are virtually identical to that of Caucasians women and are equivocally in the normal range (Table 1). Therefore, given that 1,25(OH)<sub>2</sub>D is the biologically active vitamin D, African American women are functionally vitamin D sufficient even though they have low blood levels of 25(OH)D.

25(OH)D (ng/ml)		1,25(OH) <sub>2</sub> D (pg/ml)		PTH (pg/ml)		Ca <sup>2+</sup> (mM)		Life Stage of the Subjects	Study
AA	Caucasian	AA	Caucasian	AA	Caucasian	AA	Caucasian		
18.5	29.9	-	-	40.9	36.6	-	-	Peripubertal (ages 5 to 14 years)	[26]
25.7	33.2	45.4	36.0	28.0	24.9	2.3	2.4	Adolescent (ages 11 to 15 years)	[27]
16.2	39.5	-	-	-	-	-	-	Adolescent (ages 14 to 18 years)	[28]
10.8	18.4	40.4	37.3	35.8	23.6	2.3	2.3	Adult (male and female, ages 28 to 33 years)	[29]
13.8	25.5	30.4	30.8	37.1	30.2	1.2	1.2	Premenopausal (age 25 to 40 years)	[30]
14.8	31.2			47.1	38.9	2.3	4.1		[31]
13.1	27.1	-	-	39	35.9	-	-	Pre- and post-menopausal	[32]

**Table 1:** Mean plasma levels of 25(OH)D, 1,25(OH)<sub>2</sub>D, PTH, and Ca<sup>2+</sup> in female Caucasians and African Americans (AA) reported in different studies.

The details of the statistical analysis of the data can be found in the original studies.

Reference levels of plasma PTH: 15-60 pg/ml

Reference levels of plasma Ca<sup>2+</sup>: 2.0-2.6 mM

Increased secretion of PTH into the blood circulation by the parathyroid glands is a normal physiological response to decreasing Ca<sup>2+</sup> level in the blood. PTH stimulates osteoclast-mediated bone resorption to release Ca<sup>2+</sup> and PTH stimulates activation of CYP27B1 in the kidney to catalyze the conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D, resulting in elevated blood levels of 1,25(OH)<sub>2</sub>D and increased intestinal absorption of Ca<sup>2+</sup> and renal reabsorption of Ca<sup>2+</sup> [9,10]. 1,25(OH)<sub>2</sub>D also suppresses PTH secretion by the parathyroid gland to avoid excessive bone resorption [11]. Various studies consistently show that the mean blood PTH levels of African American women are higher than that of Caucasian women (Table 1). However, although African American women have higher mean blood level of PTH than Caucasian women, the blood Ca<sup>2+</sup> levels in African American women

are in the normal range and virtually identical to that of Caucasian women (Table 1). Therefore, the normal blood calcium level indicates that the elevated blood PTH level in African American women is unlikely a condition of hyperparathyroidism, which should have caused increased bone resorption and hypercalcemia in African American women. The reason why the elevated blood PTH levels is not associated with an increased risk of bone resorption disorder in African American women is most likely due to slightly increased bone resistance to PTH in African American women [29, 30]. It is plausible that African American women also have an increased renal resistance to PTH and consequently higher blood level of PTH is needed to stimulate sufficient activity of CYP27B1 in the kidney for the production of an adequate amount of 1,25(OH)<sub>2</sub>D to ensure adequate intestinal and renal absorption of calcium.

Nevertheless, the above findings clearly demonstrate that African American women of different age groups maintain normal blood levels of the biologically active 1,25(OH)<sub>2</sub>D even though their blood 25(OH)D levels are in the deficient range (Table 1). Hence, the blood 25(OH)D level may not be the best indicator of vitamin D deficiency or sufficiency in African American women. In the future, determination of the vitamin D status in African American women, and perhaps also in African American men, should use test results that show the blood levels of 1,25(OH)<sub>2</sub>D and/or other biomarkers.

### **Relationship between the blood concentrations of 1,25(OH)<sub>2</sub>D and PTH in African American women**

Interestingly, Dawson-Hughes., *et al.* demonstrated in a study of a small group of healthy African American and Caucasian women matched with ages (ages 23 to 38 years) and body-mass index that supplementation with 0.25 µg 1,25(OH)<sub>2</sub> four times a day for 2 weeks virtually had no effect on the blood levels of 25(OH)D and Ca<sup>2+</sup> but increased the blood levels of 1,25(OH)<sub>2</sub>D and decreased blood levels of PTH in all subjects [20]. This study also demonstrated that the mean blood level of 1,25(OH)<sub>2</sub>D post treatment were almost identical between the Caucasian and African American women (40.54 + 3.65 pg/mL in Caucasian women vs 41.73 + 3.85 pg/mL in African American women). Yet, the mean post-treatment PTH level was still higher in African American women than in Caucasian women: the mean pretreatment PTH level was 31.7 + 3.8 pg/mL in Caucasians women vs 48.1 + 4.0 pg/mL in African American women while the mean post-treatment PTH level was 23.4 + 3.6 pg/mL in Caucasians women vs 33.9 + 3.7 pg/mL in African American women [20]. Therefore, it appears that African American women maintain a higher baseline level of blood PTH than the Caucasian women do. Furthermore, it is clear that the blood level of PTH is unrelated to the blood level of 25(OH)D but is inversely related to the blood level of 1,25(OH)<sub>2</sub>D. However, given that this is a study of a small number of subjects, the findings may not be generalized and they need to be confirmed in future studies involving more subjects of both genders and all age groups.

### **Normalization of the blood 25(OH)D level in postmenopausal African American women through oral vitamin D supplementation**

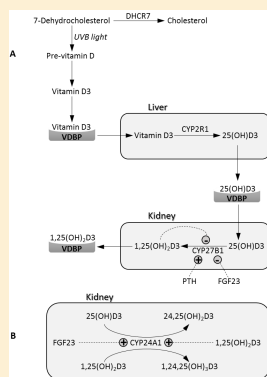
In a 3-month placebo-controlled study, Talwar *et al* demonstrated that oral supplementation with 2000 IU of vitamin D3/day to postmenopausal African American women with adequate dietary calcium intake (1200-1500 mg/day) was sufficient to raise the blood 25(OH)D level from a mean baseline of 18.76 ng/ml to a level above 20 ng/ml in 95% of the subjects of the study [33]. Similarly, Ng *et al* demonstrated that in a 4-arm, randomized, placebo-controlled study of African American men and women (ages 43-60 years), a 3-month supplement of 1000 IU vitamin D3/day, 2000 IU of vitamin D3/day or 4000 IU of vitamin D3/day raised the baseline blood 25(OH)D level from 16.2 ng/ml, 13.9 ng/ml and 15.7 ng/ml to 29.7 ng/ml, 34.8 ng/ml, and 45.9 ng/ml, respectively [34]. Furthermore, Ng *et al* suggest that an estimated 1640 IU of vitamin D3/day is needed to raise the blood 25(OH)D level over 20 ng/ml in 97.5% of subjects and 4000 IU of vitamin D3/day is needed to raise the blood 25(OH)D level equal to or above 33 ng/ml in over 80% of subjects [34]. When Gallagher., *et al.* [35] compared the effect of oral supplementation with vitamin D3 on the blood levels of 25(OH)D in vitamin D deficient Caucasian and African American women (ages 25 to 45 years) who had adequate dietary calcium intake, they found the following: 12-month supplementation with 2400 IU of vitamin D3/day raised the mean blood 25(OH)D level from 12.4 ng/ml to 43.2 ng/ml in the African American women and from 15.0 ng/ml to 39.1 ng/ml in the Caucasian women. This indicates a complete normalization in both groups [35]. Interestingly, Aloia., *et al.* [36] demonstrated that although long-term oral supplementation with vitamin D3 (800 IU of vitamin D3/day for two years, and then 2000 IU of vitamin D3/day for one year) to postmenopausal African American women (50-75 years of age) with adequate dietary calcium intake (1200-1500 mg/day) increased the blood 25(OH)D from a base line level of 18.8 ng/ml to as high as 34.8 ng/ml, the supplementation had no significant effect on bone loss or bone turnover markers in the blood [36], suggesting that the supplementation has no or little beneficial effect to the bone health of these African American women.

## **Discussion**

In the blood circulation, up to 90% of 25(OH)D is bound to VDBP (also called Gc protein encoded by the GC gene), the rest is mostly bound to albumin, and less than 1% remains free [37]. The commonly used assays that determine the concentrations of vitamin D in the blood measure the total circulating level of 25(OH)D without distinguishing the free vitamin D from the vitamin D bound to VDBP and albumin. Using a monoclonal antibody-based assay, Powe et al determined and compared the amounts of bioavailable 25(OH)D - that is, the amount of blood 25(OH)D not bound to VDBP - between African Americans and Caucasians and found that African Americans have a lower blood level of VDBP than Caucasians do and that after adjusting the VDBP-bound 25(OH)D the blood level of bioavailable 25(OH)D in African Americans is similar to that of Caucasians [38]. Powe., *et al.* explained that the lower blood level of VDBP in African Americans and high level of blood VDBP in Caucasian result in similar levels of bioavailable 25(OH)D and consequently similar blood levels of 1,25(OH)<sub>2</sub>D in both racial groups [38]. Powe., *et al.* also suggest that a measurement of the blood 1,25(OH)<sub>2</sub>D level or the amount of the bioavailable 25(OH)D in the blood would more accurately determine vitamin D sufficiency or deficiency in the African American population [38]. However, the conclusion by Powe et al needs to be re-evaluated because the monoclonal antibody-based assays they used to measure blood VDBP may not provide accurate results given that polymorphisms of VDBP are likely to interfere with the interaction between VDBP and the monoclonal antibody in their assay [39]. The GC gene that encodes VDBP has three major polymorphisms - Gc1f, Gc1s, and Gc2 - and most African Americans carry the Gc1f haplotype whereas Caucasian are most likely to carry the Gc1s haplotype [40]. Interestingly, the Gc1f form of VDBP has an increased affinity for vitamin D and thus more efficiently binds to, transports, and protects vitamin D [41]. Although the study by Powe et al seems to suggest that African American have low blood levels of VDBP when compared to Caucasian [38], recent investigations by others using a sophisticated liquid chromatography-tandem mass spectrometric assay or a polyclonal antibody-based assay for blood VDBP demonstrates that the Gc polymorphisms do not significantly affect the blood level of VDBP and that the blood levels of VDBP of African Americans are similar to that of Caucasians [39, 42]. Strikingly, studies of patients with liver diseases plus reduced blood VDBP levels [43] and the wild type and VDBP knockout mice [44] have demonstrated that the blood level of VDBP is positively correlated to the blood level of 1,25(OH)<sub>2</sub>D. Thus the recent findings by others [39, 42] showing that African Americans and Caucasians have similar blood levels of VDBP strongly suggest that the presence of adequate levels of blood VDBP is most likely a significant contributing factor for the normal levels of 1,25(OH)<sub>2</sub>D in African Americans.

Depending on the study, it is suggested that about 22% to 28% or up to 57% of the interpersonal variability of the blood 25(OH)D level among Caucasians is accounted for by genetic factors [45-47]. A genome-wide association study of 33,996 individuals of European descent identified polymorphisms in CYP2R1, VDBP, and DHCR7 to be strongly associated with vitamin D insufficiency and deficiency [48]. As illustrated in Figure 1, CYP2R1 is the enzyme that converts vitamin D to 25(OH)D and DHCR7 is the enzyme that converts the vitamin D precursor, 7-dehydrocholesterol, into cholesterol. Thus, loss-of-function mutations in CYP2R1 and gain-of-function mutations in DHCR7 are likely to cause reduced production of 25(OH)D, resulting in decreased blood levels of 25(OH)D. It is also possible that a unique polymorphism(s) in CYP24A1, which causes catabolic inactivation of vitamin D by catalyzing the conversion of 25(OH)D and 1,25(OH)<sub>2</sub>D to 24,25-dihydroxyvitamin D and 1,24,25-trihydroxyvitamin D, respectively [Figure 1B, 49, 50], can cause the low 25(OH)D status in African Americans. CYP27B1 converts 25(OH)D to 1,25(OH)<sub>2</sub>D, thus polymorphisms in CYP27B1 can also significantly influence blood levels of 25(OH)D and 1,25(OH)<sub>2</sub>D.

Interestingly, Hensen et al have recently demonstrated that the polymorphisms identified in the European descents cannot be replicated in African Americans, but the rs7041 SNP of GC is statistically, significantly associated with a low blood 25(OH)D level in African Americans [51]. However, the rs7041 SNP was previously identified by others to be associated with low blood 25(OH)D levels in both African Americans and Caucasians [52-54] and the correlation between the rs7041 SNP and the low vitamin D status in African Americans was not replicated in the study conducted by Batai et al [55]. Rather, Batai et al have found that there is a strong correlation between the rs7041 SNP and the blood 25(OH)D levels in Caucasians, while in African Americans, a strong correlation exist between a CYP2R1 SNP, rs1993116, and blood 25(OH)D level [55]. Therefore, the issue of whether there are unique polymorphisms of GC, CYP2R1, and DHCR7 gene that are responsible for the low blood level of 25(OH)D in African Americans remains to be investigated.



**Figure 1:** Metabolism of vitamin D and its regulation (A): The de novo cholesterol synthesis pathway produces 7-dehydrocholesterol, which is normally converted to cholesterol by DHCR7 (7-dehydrocholesterol reductase). In the epidermis of the skin, UV-B light causes non-enzymatic, photochemical conversion of 7-dehydrocholesterol to previtamin D<sub>3</sub>, which then spontaneously isomerizes into vitamin D<sub>3</sub>. Vitamin D<sub>3</sub> is secreted into the blood circulation. Vitamin D<sub>3</sub> is absorbed by the liver from the blood circulation and then converted to 25(OH)D<sub>3</sub> through a reaction catalyzed by the enzyme CYP2R1 (also called vitamin D 25- $\alpha$ -hydroxylase). The resulting 25(OH)D<sub>3</sub> is secreted back to the blood circulation. Upon stimulation by PTH (parathyroid hormone), the kidneys convert 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub> via the reaction catalyzed by the enzyme CYP27B1 (also called 1- $\alpha$ -hydroxylase). The resulting 1,25(OH)<sub>2</sub>D<sub>3</sub> is secreted into the blood circulation. In the blood, the vitamin D molecules are carried by the VDBP (vitamin D-binding protein). PTH positively (+) whereas 1,25(OH)<sub>2</sub>D<sub>3</sub> and FGF23 negatively (-) regulates the CYP27B1 activity in the kidney, thereby regulating the production of 1,25(OH)<sub>2</sub>D<sub>3</sub>. 25(OH)D<sub>3</sub> is the predominant form of vitamin D in the blood and is measured in lab tests for the determination of vitamin D status [3]. (B) CYP24A1 (also called 24-hydroxylase) is the enzyme that catalyzes catabolic inactivation of both 25(OH)D<sub>3</sub> and 1,25(OH)<sub>2</sub>D<sub>3</sub>. FGF23 and 1,25(OH)<sub>2</sub>D<sub>3</sub> independently have positive regulatory effect on CYP24A1 activity [12, 13, 60].

Nevertheless, there is a small body of evidence suggesting that there are unique genetic factors in African Americans that regulate vitamin D metabolism. First, a study by Signorello, et al. determined that based on the analysis of a panel of 276 ancestry informative SNPs, there was a statistically significant linear decrease in the blood level of 25(OH)D with increasing African ancestry [56]. Thus, individuals with high African ancestry (>95%) have a mean of 16.5 ng/mL 25(OH)D whereas people with lower African ancestry (< 85%) have 1.2 times more circulating 25(OH)D [56]. Secondly, it was estimated that two single nucleotide polymorphisms of the GC gene and one in CYP27B1 gene were strongly related to the blood 25(OH)D level in African Americans [57]. The highest genotype score among African Americans was associated with an average reduction of 7.1 ng/ml in the level of blood 25(OH)D [57].

Given that FGF23 is an important regulator of CYP24A1 [12,13,60] and that the expression of the CYP24A1 gene, which is normally at very low level, is strongly up-regulated by 1,25(OH)<sub>2</sub>D [58,59] or FGF23 [60], it will be important to determine and compare the relationship between the blood level of FGF23 and the blood levels of various forms of vitamin D in African Americans and Caucasians. It has been suggested that a unique variant of the vitamin D responsive element (VDRE) that weakens the transcriptional activity of the promoter of the CYP24A1 gene exists within the African American population [61]. Future research is needed to investigate unique genetic polymorphisms that may be specifically associated with the a low blood level of 25(OH)D yet a normal blood level of 1,25(OH)<sub>2</sub>D in African American women and most likely also in African American men.

In summary, although vitamin D deficiency is defined as the blood level of 25(OH)D lower than 20 ng/mL [16], this classification of vitamin D deficiency may not be applicable to African American women because they have normal blood levels of 1,25(OH)<sub>2</sub>D and normocalcemia despite the fact that their blood 25(OH)D level is in the range of deficiency (Table 1). Given that it is unclear whether the observed low blood level of 25(OH)D and normal blood level of 1,25(OH)<sub>2</sub>D in African American women in different studies is just a short-term phenomenon observed at the end of each study or a long-term phenomenon, it will be critical to use well-designed, long-term, prospective cohort studies of large numbers of African American women (as well as African American men) with a low blood level of 25(OH)<sub>2</sub>D and a normal blood levels of 1,25(OH)<sub>2</sub>D to investigate if a chronic low 25(OH)D vs normal 1,25(OH)<sub>2</sub>D status can be consistently maintained in the absence of bone disorders as well as other negative health outcomes, including premature mortality, autoimmune diseases, diabetes, chronic musculoskeletal pain, neurological and cognitive disorders, depression, and dental disease [3, 62, 63].

## Conflict of Interest

The authors declare that there is no conflict of interest that would cause the impartiality of this review.

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