Is There Pandemic Vitamin D Deficiency in the Black Population? A Review of Evidence

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Abstract: Although 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] is the biologically active form of vitamin D, measurement of the total serum 25-hydroxyvitamin D [25(OH)D] level is the gold standard used to define vitamin D status. Currently, it is widely accepted that serum 25 (OH) D levels below 20 ng/ml defines vitamin D deficiency. According to this definition, there appears to be pandemic vitamin D deficiency in the Black population. However, there is no evidence of higher-than-normal rates of common complications and symptomology of true vitamin D deficiency in the Black population. What is going on? We researched the MEDLINE databases to find studies, from 1967 to present, that directly compare between Blacks and Caucasians the following: serum vitamin D level, serum calcium level, serum parathyroid hormone level, bone mineral density and health, and non-skeletal risks associated with vitamin D deficiency. The available studies consistently show that Blacks tend to have serum 25(OH)D levels in the deficient range while their serum 1,25(OH)$_2$D level is similar to, if not even slightly higher than that of Caucasians, and that the serum Ca^{2+} level in Blacks is virtually identical to that in Caucasians. Therefore, it appears that the serum 25(OH)D level is not the best marker of vitamin D sufficiency or deficiency in Blacks. In the future, clinical evaluation of the vitamin D status in the Black population needs to consider other serum biomarkers such as 1,25(OH)$_2$D and/or bioavailable 25(OH)D.

Keywords: Black, deficiency, health, vitamin D.

INTRODUCTION

There are two sources of vitamin D for the human body: diet and biosynthesis of vitamin D in the skin upon exposure to adequate UV-B rays. As illustrated in Fig. (**1**), irradiation of the epidermis of the skin by UV-B rays induces a non-enzymatic reaction that converts 7-dehydrocholesterol to previtamin D. The previtamin D then undergoes a slow, spontaneous conversion to vitamin D$_3$. Vitamin D$_3$ is transported out of the skin and undergoes two rounds of hydroxylation reactions; the first in the liver and the second in kidney. In the liver, vitamin D$_3$ is converted to 25(OH)D$_3$ by the enzyme, 25-hydroxlylase. In the kidney, the 25(OH)D$_3$ is converted to the biologically active 1,25(OH)$_2$D$_3$ by the enzyme, 25-hydroxycalciferol 1-α-hydroxylase (1-α-hydroxylase) in the proximal convoluted tubule [1]. Dietary sources contain vitamin D$_3$ and vitamin D$_2$. Metabolism of vitamin D$_2$ in the human body is the same as that of vitamin D$_3$. In general, hydroxylated metabolites of vitamin D$_2$ and vitamin D$_3$ are simply referred to as 25(OH)D and 1,25(OH)$_2$D. It should be noted that

1,25(OH)$_2$D is the biologically active vitamin D and that the biological effect of 1,25(OH)$_2$D on cells is mediated by the vitamin D receptor (VDR), a specific ligand-dependent nuclear transcription factor that regulates expression of a large number of genes in many organs including bone, muscle, pancreas, brain, the pituitary, and the immune system [2, 3].

The melanin pigment is an excellent natural absorbent of the UV-B radiation, and therefore dark-skinned people require substantially more exposure to UV-B rays than fair skinned people in order to synthesize an adequate amount of vitamin D$_3$ [4, 5]. Thus, dark-skinned people, such as Blacks and dark skinned Indians, are more susceptible to developing vitamin D deficiency in the absence of adequate sunlight exposure or without taking vitamin D supplements [4-7]. The significance of adequate sunlight exposure for the vitamin D status in dark-skinned people is best illustrated by a recent finding showing that those Africans, such as the Maasai and Hadzabe people, who still maintain a hunter-gather life style and get plenty of sunlight exposure, have a serum level range of 25(OH)D at 43 ng/mL to 59 ng/mL [8], a concentration range that can only be found in sunlight-replete Caucasians lifeguards in the summer [9].

The conversion of 25(OH)D to 1,25(OH)$_2$D by the 1-α-hydroxylase in the kidney is strictly regulated (Fig. **1**). The activity of 1-α-hydroxylase is stimulated primarily by

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parathyroid hormone (PTH) and inhibited by phosphate, Ca^{2+}, and fibroblast growth factor 23 (FGF23). In addition, 1-α-hydroxylase is subjected to feedback inhibitory regulation by 1,25(OH)$_2$D. At high concentrations, 1,25(OH)$_2$D induces inhibition of its own synthesis by down-regulating 1-α-hydroxylase activity in the kidney and activating vitamin D 24 hydroxylase in peripheral tissues (Fig. **1**). The 24-hydroxylase hydroxylates both 25(OH)D and 1,25(OH)$_2$D on the #24-carbon to yield biologically inactive 24-hydroxyl derivatives, 24,25-dihydroxy-vitamin D [24,25(OH)$_2$D] and 1,24,25-trihydroxyvitamin D [1,24,25 (OH)$_3$D] [11, 12]. The combined actions of PTH, FGF23, 1,25(OH)$_2$D, Ca^{2+} and phosphate on the vitamin D metabolic enzymes lead to homeostasis of 1,25(OH)$_2$D, which is important for the maintenance of calcium and phosphate homeostasis in the blood.

The classical function of vitamin D is to regulate calcium and phosphorus homeostasis in the blood, which is critical for bone health. Thus, clinical determination of vitamin D status is largely based on the relationship between serum 25(OH)D level and bone disorders [13]. However, epidemiological studies have linked vitamin D deficiency with a plethora of negative health outcomes, including cardiovascular diseases, immune dysfunction, cancer, reproductive disorders, neurological disorders, and metabolic syndromes [13-16]. The action mechanism of the biologically active vitamin D, 1,25(OH)$_2$D, involves nuclear vitamin D receptor (VDR) which is ubiquitously expressed and acts as ligand-dependent transcription factor that regulates the promoters of vitamin D target genes via binding to the vitamin D responsive element (VDRE) in the promoters of these genes [17]. Most cell types in the human body appear to respond to 1,25(OH)$_2$D stimulation, and a large number of the genes in the human genome are regulated by 1,25(OH)$_2$D [2, 3]. In this context, it is frightening to see that up to 82.1% Blacks in the US are considered to be vitamin D deficient as defined by less than 20 ng/mL 25(OH)D in the serum [18]. Fortunately, there is no evidence of high rates of medical complications and symptomology of true vitamin D deficiency in the US Black population. What is going on? To understand it, we researched the MEDLINE databases to find studies, from 1967 to present, that directly compare between Blacks and Caucasians the following: serum vitamin D level, serum calcium level, serum parathyroid hormone level, bone mineral density and health, and non-skeletal risks associated with vitamin D deficiency. To our knowledge, this is the first attempt to systematically review the biomedical literature concerning specifically the vitamin D status in Blacks. In this review, we report on the available information and suggest that this pandemic vitamin D deficiency in the black population is a false alarm, because most Blacks of both genders and at all age groups have healthy serum levels of the biologically active 1,25(OH)$_2$D and they are functionally vitamin D sufficient despite the fact that their serum 25(OH)D levels are in the deficient range.

REVIEW OF EVIDENCE

Blacks Are Deficient in 25(OH)D but Replete with 1,25(OH)$_2$D

In the blood circulation, up to 90% of 25(OH)D is bound to vitamin D-binding proteins (VDBP), the rest is mostly bound to albumin, and less than 1% remains free [10]. The 25(OH)D circulates in the blood at ng/mL concentrations
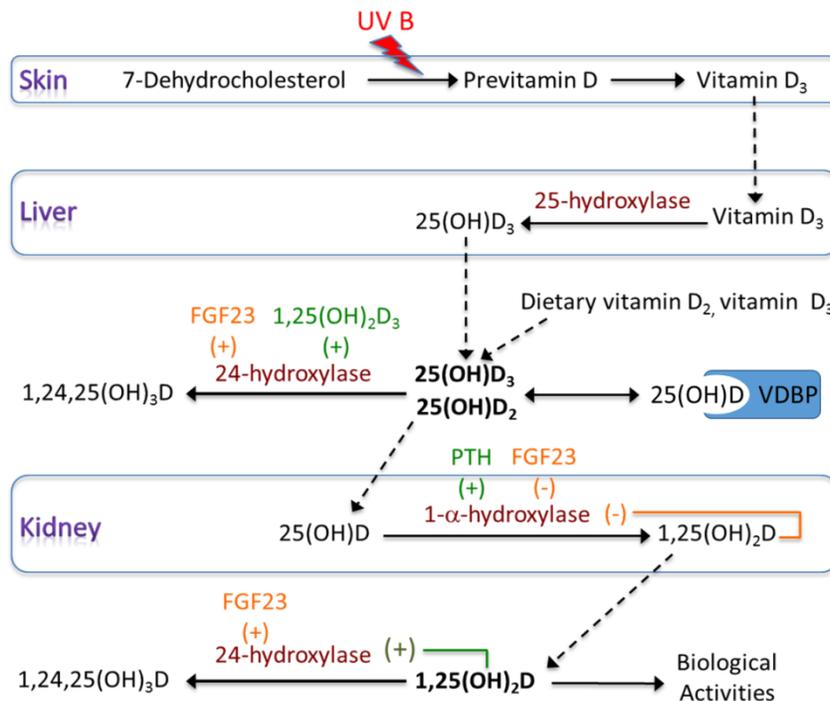
(+), stimulatory effect; (-), inhibitory effect; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23

Fig. (1). Metabolism of vitamin d in human body.

and has a half-life of approximately 15 days whereas the $1,25(OH)_2D$ circulates at pg/mL concentrations and has a half-life of approximately 15 hours [19-21]. Even though $1,25(OH)_2D$ is the biologically active form of vitamin D, determination of vitamin D status has been all about measuring the total serum levels of 25(OH)D for both technical convenience and the fact that the serum level of 25(OH)D is largely proportional to the serum level of $1,25(OH)_2D$ in the general non-black population. The available studies have consistently demonstrated that many Blacks of both genders and at all life stages – neonates, preadolescents, adolescents, middle ages, and old ages – have serum 25(OH)D levels in the ranges of deficiency (Table **1**). However, studies that have directly compared the serum levels of both 25(OH)D and $1,25(OH)_2D$ between Blacks and Caucasians consistently found that the serum $1,25(OH)_2D$ level in Blacks is similar if not even slightly higher than that in Caucasians, notwithstanding the deficiencies of 25(OH)D (Table **1**). These data indicate that Blacks are by large replete with the biologically active vitamin D and therefore are not functionally vitamin D deficient and that low serum 25(OH)D level in Blacks is not indicative of vitamin D deficiency.

Bioavailability of Serum 25(OH)D in Blacks

The commonly used assays that determine the concentrations of vitamin D in the serum measure total circulating 25(OH)D without distinguishing the free vitamin D from the vitamin D bound to vitamin D binding protein (VDBP) and albumin. Recently, Powe *et al.* [22] determined and compared the amounts of bioavailable 25(OH)D – that is, the amount of serum 25(OH)D not bound to VDBP – between Blacks and Caucasians and found the following: (i) the amount of bioavailable serum 25(OH)D is proportional

to the total amount of 25(OH)D in Caucasians; (ii) Blacks have vitamin D deficiency as defined by the low serum 25(OH)D level; (iii) Blacks have lower serum VDBP level than Caucasians; and (iv) the serum bioavailable 25(OH)D level in Blacks is similar to that of Caucasians after adjusting the VDBP-bound 25(OH)D. This study explains that one reason why Blacks have healthy levels of serum $1,25(OH)_2D$ is because they have adequate levels of bioavailable 25(OH)D in the serum due to decreased serum VDBP level. Hence, it appears that although it is not necessary for Caucasians, a measurement of the serum $1,25(OH)_2D$ level or the amount of the bioavailable 25(OH)D in the serum would more accurately determine vitamin D sufficiency or deficiency in the Black population. This is very important given the fact that these days taking high doses of oral vitamin D supplements is the norm of life for people who are diagnosed to be vitamin D deficient, and that excessive intake of vitamin D has the potential to cause chronic toxic effects of hypervitaminosis D, which presents as hypercalcemia and renal damage [23-25]. It is not unreasonable to think that treatment of the traditionally determined "vitamin D deficient" Blacks may cause a severe toxicity of hypervitaminosis D.

PTH Status, Calcium Homeostasis and Bone Health in Blacks

The classical function of $1,25(OH)_2D$ is its ability to act in the intestine to stimulate the absorption of calcium and phosphorous, and in the kidney to stimulate the reabsorption of calcium and phosphorus. Thus, chronic deficiency of $1,25(OH)_2D$ in the body due to various reasons, such as loss-of-function mutations in 1-α-hydroxylase deficiency and hypoparathyroidism, results in bone disorders, such as rickets, osteoporosis and osteomalacia. Elevation of the blood PTH level is a normal physiological response to

Table 1.   Comparison of the mean blood levels of 25(OH)D, $1,25(OH)_2D$, PTH, and calcium (Ca^{2+}) in caucasians and blacks.

25(OH)D (ng/mL)		1,25(OH)$_2$D (pg/mL)		PTH (pg/mL)		Serum Ca^{2+} (mM)		Subject Characteristics	Reference
Caucasian	Black	Caucasian	Black	Caucasian	Black	Caucasian	Black		
29.9	18.5	N/A	N/A	36.6	40.9	N/A	N/A	Peripubertal females	[44]
27.16	13.1	N/A	N/A	35.9	39	N/A	N/A	Adult females	[46]
31.2	14.8	N/A	N/A	38.89	47.08	4.125	2.29	Adult females	[48]
33.2	25.7	36.0	45.4	24.9	28.0	2.38	2.32	Young females	[49]
18.4	10.8	37.31	40.38	23.58	35.83	2.32	2.29	Adult males and females	[34]
25.5	13.8	28.43	28.03	30.27	37.15	1.20	1.21	Adult females	[33]
17.41	11.71	31.45	32.22	N/A	N/A	N/A	N/A	Neonates	[47]
32.6	20.4	N/A	N/A	N/A	N/A	N/A	N/A	Adult males	[22]
29.3	19.1	N/A	N/A	N/A	N/A	N/A	N/A	Adult females	
36.66	21.15	N/A	N/A	N/A	N/A	N/A	N/A	Adolescent males	[45]
39.54	16.23	N/A	N/A	N/A	N/A	N/A	N/A	Adolescent females	

The details of the statistical analysis of the data shown here can be found in the original studies. N/A: not available
Normal PTH levels: 15-60 pg/ml
Normal calcium levels: 2.0-2.6 mM

decreased calcium level in the blood. The primary functions of PTH include stimulation of bone resorption by osteoclasts to release calcium from the bone and stimulation of 1-α-hydroxylase in the kidney to increase the production of 1,25(OH)$_2$D, which in turn stimulates intestinal absorption of calcium and renal reabsorption of calcium.

In comparison to the serum PTH level in Caucasians, the serum PTH level in Blacks are approximately 15% higher, a common findings in different studies (Table **1**). However, the serum Ca^{2+} level in Blacks is in the normal range and virtually identical to that of Caucasians (Table **1**), indicating that the elevated serum PTH level in Blacks is not indicative of clinical hyperparathyroidism because hypercalcemia normally occurs as a result of hyperparathyroidism [26-28].

Although high serum PTH level increases the risk of accelerated rate of bone resorption and bone disorders in Caucasians, the higher serum PTH level in Blacks actually does not seem to cause bone disorders. As a matter of fact, Blacks actually have higher bone mass density (BMD), higher bone strength and less risk of bone fracture than Caucasians as shown in studies conducted by Dawson-Hughes *et al.* [29] and Hochberg [30]. For example, the risk that a postmenopausal Caucasian woman having a hip fracture by age 80 is 11% compared with only 4% for a Black woman [31, 32]. Apparently, the higher PTH level does not cause faster bone turnover in Blacks possibly as a result of bone resistance to PTH [33, 34]. This bone resistance to PTH is likely to be beneficial to the health of the skeletal system in Blacks since it prevents PTH from overly stimulating bone resorption when serum PTH level is high. Nevertheless, the relationship between serum PTH level and vitamin D metabolism seems greatly different between Blacks and Caucasians [35].

Effect of 1,25(OH)$_2$D on Serum PTH Level in both Blacks and Caucasians

True vitamin D deficiency can decrease the serum calcium level, which in turn can cause secondary hyperparathyroidism and increased bone resorption [27]. Thus, the increase of serum PTH level is a normal compensatory mechanism in response to a decreasing serum calcium concentration. But, why do Blacks have elevated serum PTH level and yet their serum levels of Ca^{2+} are within the normal range? The answer to this question is provided by a study involving female Black and Caucasian

subjects matched with ages and body-mass index. In this study, the subjects received 0.25 μg 1,25(OH)$_2$D four times a day for 2 weeks. At the end of this study, it was found that the treatment virtually had no effect on the serum levels of 25(OH)D and Ca^{2+}, it increased the serum 1,25(OH)$_2$D level, and it significantly decreased the serum PTH level in all subjects (Table **2**) [29]. Furthermore, this study demonstrated that the treatment caused the average serum levels of 1,25(OH)$_2$D in these female Caucasians and Blacks to be increased to an almost identical level (40.54 $\pm$ 3.65 pg/mL in Caucasians vs 41.73 $\pm$ 3.85 pg/mL in Blacks), and yet the post treatment level of PTH still remained higher in Blacks than in Caucasians: the pretreatment PTH levels are 31.7 $\pm$ 3.8 pg/mL in Caucasians vs 48.1 $\pm$ 4.0 pg/mL in Blacks and the post treatment PTH levels are 23.4 $\pm$ 3.6 pg/mL in Caucasians vs 33.9 $\pm$ 3.7 pg/mL in Blacks (Table **2**). These findings demonstrated two important points: first, these Black women maintain a higher level of serum PTH than Caucasian women do even when their serum 1,25(OH)$_2$D levels are almost identical; second, changes in the serum levels of PTH is unrelated to the status of calcium and 25(OH)D but directly related to the 1,25(OH)$_2$D level in the blood. Since PTH directly affects the production of 1,25(OH)$_2$D in the kidney by increasing the level of renal 1α-hydroxylase [36] and since 1,25(OH)$_2$D can directly induce suppression of the expression of PTH gene in and secretion of PTH from the human parathyroid glands [37], it is plausible that there is a Ca^{2+}-independent 1,25(OH)$_2$D $\rightarrow$ PTH regulatory loop that regulates the serum 1,25(OH)$_2$D level. Thus, PTH would stimulate 1-α-hydroxylase for 1,25(OH)$_2$D synthesis and at high concentrations, 1,25(OH)$_2$D would exert a feedback inhibitory effect on the expression of PTH gene in and secretion of PTH from the parathyroid glands in a Ca^{2+}-independent manner. However, there is likely a caveat about this 1,25(OH)$_2$D $\rightarrow$ PTH loop in Blacks – that is, like the bone resistance to PTH [33, 34], there could also be kidney resistance to PTH in Blacks. Such a kidney desensitization to PTH can explain why the serum PTH level in Blacks is higher than that in Caucasians even when the 1,25(OH)$_2$D levels are almost identical in both groups because higher levels of PTH are needed to maintain an adequate level of the 1-α-hydrolylase in the kidney to maintain sufficient amount of 1-α-hydroxlylase for the synthesis of the same amount of 1,25(OH)$_2$D in the bodies of Blacks. However, future research involving more subject and subjects of both genders and at different age groups is needed to investigate this possibility.

Table 2. **Effects of 1,25(OH)$_2$D treatment on the serum levels of 25(OH)D, 1,25(OH)$_2$D, PTH, and calcium (Ca^{2+}) in adult female caucasians and blacks.**

Conditions	25(OH)D (ng/mL)		1,25(OH)$_2$D (pg/mL)		PTH (pg/mL)		Serum Ca^{2+} (mM)		Reference
	Caucasian	Blacks	Caucasian	Blacks	Caucasian	Blacks	Caucasian	Blacks	
Before treatment	35.4 ($\pm$ 3.7)	19.8($\pm$ 3.9)	30.08 ($\pm$ 2.38)	36.81 ($\pm$ 2.46)	31.7 ($\pm$ 3.8)	48.1 ($\pm$4.0)	2.24 ($\pm$ 0.02)	2.21 ($\pm$ 0.02)	[29]
After treatment	38.7 ($\pm$ 4.9)	21.7 ($\pm$5.2)	40.54 ($\pm$ 3.65)	41.73 ($\pm$ 3.85)	23.4 ($\pm$ 3.6)	33.9 ($\pm$3.7)	2.27 ($\pm$ 0.02)	2.23 ($\pm$ 0.02)	

Normal PTH levels: 15-60 ng/ml
Normal calcium levels: 2.0-2.6 mM

Vitamin D Status and the Risks of Non-skeletal Diseases in the Black Population

Various epidemiological studies have associated low serum 25(OH)D level with negative health outcomes in the general population [13-16]. In addition to causing bone disorders, vitamin D deficiency is also associated with increased risks of developing stroke, coronary heart disease, premenstrual syndrome, chronic kidney disease, and systolic high blood pressure in Caucasians (Table **3**). However, direct comparison between Caucasians and Blacks indicate that Blacks are relatively protected from the numerous clinical complications of the non-skeletal systems (Table **3**).

DISCUSSION

In general, vitamin D deficiency is defined as the serum level of 25(OH)D lower than 20 ng/mL and closely associated with clinical bone disorders, such as rickets, osteomalacia and osteoporosis. However, this classification of vitamin D deficiency is most unlikely to be applicable to Blacks because they have healthy serum levels of the biologically active $1,25(OH)_2D$ and calcium at all life stages despite the fact that their serum 25(OH)D level is in the range of deficiency. Blacks also do not present with high rates of the various skeletal and non-skeletal clinical complications associated with true vitamin D deficiency (Tables **1** and **3**). Therefore, the low serum 25(OH)D level and normal serum $1,25(OH)_2D$ level in Blacks are indicative of functional vitamin D sufficiency. This feature is rather unique to Blacks because the serum 25(OH)D level is proportional to the serum level of $1,25(OH)_2D$ and deficiency of 25(OH)D is indicative of functional vitamin D deficiency in people of other races. For instance, the high rate of vitamin D deficiency in the Indian population is closely associated with high incidences of bone disorders [50]. Nevertheless, we believe determination of the vitamin D status in Blacks in the future should use test results that show the serum levels of bioavailable 25(OH)D and $1,25(OH)_2D$.

A study by Signorello et al. determined serum 25(OH)D level of an African American population in the context of the African ancestry based on the analysis of a panel of 276 ancestry informative SNPs found that, with increasing African ancestry, there is a linear statistically significant decrease in the serum level of 25(OH)D [38]. In this study, individuals with high African ancestry, (>95%) have 16.5 ng/mL 25(OH)D whereas people with lower African ancestry, (<85%) have 1.2 times more circulating 25(OH)D. It is most likely that the evolution of African people has selected an adaptive compensatory mechanism to cope with a reduced synthesis of previtamin D in the skin due to skin hyperpigmentation that reduces the amount of UV-B radiation that could reach the epidermis [5, 39]. This compensatory mechanism maximizes the synthesis and maintenance of optimal serum levels of $1,25(OH)_2D$ in the face of low serum 25(OH)D level. The outcome is successful maintenance of calcium homeostasis and the health of the skeletal system as well as the non-skeletal systems. It is most likely that the evolution of this mechanism has involved the selection of multiple changes. First, there is the lowering of the concentrations of VDBP in the blood to increase the bioavailability of 25(OH)D for the synthesis of $1,25(OH)_2D$ [22]. Second, there is elevation of the serum PTH to high enough levels to perhaps stimulate and maintain high amounts of 1-α-hydrolylase in the kidney for the synthesis of adequate amounts of $1,25(OH)_2D$. Yet, the levels of PTH are not too high to causes bone resorption and complications of hyperparathyroidism. Third, the 24-hydroxylase catalyzes the conversion of $1,25 (OH)_2D$ into the inactive intermediate $1,24,25(OH)_3D$ [12]. The 24-hydroxylase gene is normally expressed at very low level, but its expression is strongly up-regulated by $1,25(OH)_2D$ [40]. It has been demonstrated that a unique variant of the vitamin D responsive element (VDRE) that weakens the transcriptional activity of the promoter of the 24-hydroxylase gene exists in the Black population [41]. The consequence of the presence of this variant is that the expression of the 24-hydroxylase gene is not so robust even in the presence of high concentrations of $1,25(OH)_2D$ [41]. This change ensures slower rate of inactivation of $1,25(OH)_2D$ in Blacks.

CONCLUSION

In summary, it is critical to investigate why Blacks are able to maintain a healthy serum $1,25(OH)_2D$ level at all life stages despite the fact that they have deficient 25(OH)D level (Table **1**). Accurate determination of vitamin D status in Blacks will be beneficial for the management of their overall health since true vitamin D deficiency is correlated to, if not the cause of, a long list of negative health outcomes, including premature mortality, cancers, autoimmune diseases, diabetes, chronic musculoskeletal pain, neurological and cognitive disorders, depression, dental

Table 3.   Relationship between various disease risk and low levels of 25(OH)D in caucasians and blacks.

Diseases	Risk Associated with Low 25(OH)D Level		Reference
	Caucasian	**Blacks**	
Stroke	Increased risk	No apparent association	[51]
CHD	Increased risk	No apparent association	[52]
PMS	No apparent association	No apparent association	[53]
CKD	Increased fatality	No apparent association	[54]
HBP	Increased risk	No apparent association	[55]

CHD: Coronary Heart Disease; PMS: Premenstrual Syndrome; CKD: Chronic Kidney Disease; HBP: systolic High Blood Pressure.

disease and cardiovascular disease [42, 43]. It is therefore of utmost importance that future research be focused on better understanding of the mechanisms that regulate metabolism of vitamin D and maintain a healthy serum $1,25(OH)_2D$ level in Blacks.

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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