Moving Points in Nephrology

Vitamin D, Blood Pressure, and African Americans: Toward a Unifying Hypothesis

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Vitamin D deficiency has increasingly been recognized in the general population and especially in African Americans whose deep skin pigmentation makes vitamin D photosynthesis inefficient. Over the last decade there has been increasing interest in the role that vitamin D deficiency may play in BP modulation because many epidemiologic studies have shown an inverse association between serum vitamin D concentration and BP. There is a high prevalence of vitamin D deficiency in African Americans who also have an increased susceptibility to develop hypertension and its consequences. This paper will review the circumstances leading to vitamin D deficiency in the African American population and will also discuss how vitamin D deficiency can affect the renin-angiotensin system, free radical production, inflammatory processes, and carbohydrate tolerance that in turn influence vascular endothelial function and vascular structure producing increased vascular resistance. It will speculate that the presence of vitamin D deficiency throughout life from its earliest phases may adversely affect the microvasculature in African Americans, thereby playing a major role in the genesis and maintenance of hypertension.

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Numerous studies across several disciplines have demonstrated that the vitamin D receptor (VDR) and the 1,α-hydroxylase enzyme are found in many tissues and that VDR activation can modulate a variety of physiologic processes in addition to its classical endocrine effects on calcium and parathyroid hormone (PTH) homeostasis and bone mineralization. This has led to an increasing interest in the possible role of vitamin D, the VDR, and 1,α-hydroxylase in the pathogenesis of a number of disease states. Because the VDR and 1,α-hydroxylase are found in vascular endothelial and smooth muscle cells (VSMC) and because vitamin D deficiency is found to occur frequently in the general population, an association of vitamin D deficiency with cardiovascular disease, renal disease, and hypertension is gaining acceptance. Because it has long been observed that African Americans have a higher prevalence of hypertension when compared with Caucasians and because of their high prevalence of vitamin D deficiency, this paper will focus on the role vitamin D deficiency may play in the pathogenesis and maintenance of hypertension as it relates to people of the African Diaspora. Much of what will be discussed also applies to Caucasians but the consequences affect a greater proportion of African Americans, creating a disproportionate risk.

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Vitamin D, Ultraviolet (UVB) Light, and BP

Most Africans and others with deep skin pigmentation live at or near the equator. Compared with those living at more northern or southern latitudes, native Africans and other people of color living near the equator have a lower prevalence of hypertension (1–3). We have demonstrated that for each 10° north or south of the equator BP increases by 2.5 mmHg and hypertension prevalence by 2.5% (1). Because available UVB light decreases progressively at increasing distances from the equator, cutaneous vitamin D photosynthesis is progressively limited (4,5). This is particularly problematic for Africans because their high skin melanin content impairs the efficiency of cutaneous vitamin D photosynthesis and at long distances from high UVB regions this limitation is magnified (6). Thus, studies have reported that when compared with Europeans, Africans and other people of color have a significantly higher prevalence of vitamin D deficiency (7–10). Because BP has been shown to vary inversely with UVB light availability and because people of color have a high prevalence of low circulating levels of 25-hydroxyvitamin D3 (25(OH)D3), it has seemed reasonable to speculate that vitamin D deficiency may contribute to their increased prevalence of hypertension. In this regard, these studies (7–10) have reported inverse associations between BP and blood concentrations of 25(OH)D3 and one (8) has suggested that about half the BP difference noted between African Americans and European Americans could be explained by vitamin D deficiency. Although these statistical associations may suggest causality, they do not prove it. However, a relationship between cutaneous vitamin D photosynthesis and BP has been directly confirmed experimentally by Krause *et al.*

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who found UVB irradiation not only significantly increased 25(OH)D3 concentrations but also lowered BP, an effect not seen with exposure to UVA radiation (11). Thus, the question remaining to be answered is by what mechanism(s) do(es) vitamin D deficiency contribute to hypertension risk in African Americans. The answer may lie in the effects of vitamin D deficiency on arteries and arterioles.

Vitamin D and VDR Activation and Microvascular Disease

There is considerable evidence to support the view that hypovitaminosis D may be important in the pathogenesis of vasculopathy that contributes to the development of hypertension in African Americans.

Vitamin D and the Renin-Angiotensin System

Twenty-five years ago Resnick *et al.* (12) demonstrated an inverse association between $25(OH)D_3$, 1,25-(OH)2 vitamin D3 (1,25(OH)2D3), and plasma renin activity in hypertensive patients. More recently, Li *et al.* (13) demonstrated hypertension, increased expression of renin mRNA, and increased angiotensin II (Ang II) in a VDR knockout mouse model. These changes were independent of calcium metabolism and the effects on renin and Ang II were reversed by 1,25(OH)2D3 bound to VDR. The BP effect was also reversed with angiotensin-converting enzyme inhibition but not by 1,25(OH)2D3 alone. Subsequent studies proved the effect was independent of PTH (14). In other studies, Ang II was shown to increase renal arteriolar tone by stimulating calcium entry and storage in vascular endothelial and smooth muscle cells (15). It may also promote VSMC growth and smaller lumen calibers affecting renal blood flow and renal vascular resistance, changes reversed by angiotensin-converting enzyme inhibition (16). Moreover, hypertension and renin-angiotensin system (RAS) upregulation were also found in 1,α-hydroxylase knockout mice, effects that could be corrected with 1,25(OH)2D3 (17).

The stimulatory effect of vitamin D deficiency on RAS may induce BP-independent Ang II–mediated inflammatory responses and vascular growth (18). Ang II upregulates extracellular matrix proteins and promotes fibrosis of VSMC by upregulating TGFβ1, thereby converting VSMC to myofibroblasts and producing vascular stiffness (19). 1,25(OH)2D3 has been shown to suppress these effects by downregulating renin mRNA, by inducing hepatocyte growth factor expression, and by blocking activation of pro-inflammatory transcription factors such as NF-κB (20,21). These findings may relate to vascular changes observed in African Americans for it has been observed that TGFβ1 is overexpressed in African Americans (22).

Increased Ang II expression may also induce oxidative stress in VSMCs by increasing NAD(P)H oxidase activity, producing reactive oxygen species that can affect a multitude of processes including the following: cell growth and migration, including vascular proliferation and hypertrophy, inflammation and extracellular matrix production, including TGFβ1, ion channels, and endothelial fibrosis and dysfunction (23,24).

1,25(OH)2D3 may also exert its effects on vascular structure and function independent of the RAS. It has been shown to mediate endothelium-dependent vasodilation by increasing expression of vascular endothelial growth factor that can upregulate endothelial nitric oxide synthase and also stimulate VSMC proliferation (25). 1,25(OH)2D3 also produces VSMC vasodilation by stimulation of prostacyclin production (26) and by reducing endothelium-dependent VSMC contractions by reducing influx of calcium into endothelial cells (27).

In experimental studies 1,25(OH)2D3 induces osteoblastic differentiation in human and bovine vascular smooth muscle. Active vitamin D also increases calcium uptake in aortic smooth muscles, although this finding is not true in all tissues. However, in humans clinical studies show an inverse association between vascular calcification and 1,25(OH)2D3 (28). Thus, increased vascular calcium content may partly explain the inverse association of vascular stiffness with 25(OH)D3 and 1,25(OH)2D3 manifested by increased pulse wave velocity and blunted flow-mediated dilation (29).

Characteristics of Resistance Vessels in African Americans

There are significant differences between African Americans and Caucasians with regard to microvascular structure and function; these include increased systemic and renal vascular resistance and decreased renal blood flow (RBF) (30) that may be attributed to activation of the RAS (31). Attenuated endothelium- and nonendothelium-dependent vasodilation has been noted to be manifested by blunted isoproterenol-mediated vasodilation (32) as well as attenuated flow-mediated and nitroglycerin-induced vasodilation (33). This vascular stiffness has been seen at an early age (34) and may precede the onset of hypertension or else is independent of BP.

Differences in microvascular structure such as retinal arteriolar lumen narrowing (35), intima/media fibrosis, and reduced lumen diameters of renal arterioles are seen more frequently in African Americans than in Caucasians (36–38). These, too, have been found to be independent of BP and are felt to predict future hypertension. These structural and functional changes may contribute to the development of hypertension and to secondary glomerulosclerosis so frequently seen in hypertensive African Americans (38) and may be related to the vascular effects of vitamin D deficiency described above.

Vitamin D, Calcium Homeostasis, and Parathyroid Hormone

The foregoing suggest an independent role for vitamin D and VDR activation on vascular structure and function but in whole animals one cannot ignore the fact the vitamin D deficiency stimulates PTH secretion. Thus, its effects must also be considered. It is known that in African Americans PTH is inversely associated with 25(OH)D3 and is significantly higher than in Caucasians (39). Although short-term exposure to PTH can produce vasorelaxation, long-term exposure is associated with elevated BP. PTH-induced hypertension may be mediated by increasing intracellular calcium concentration, blunting endothelial function, and stimulating vascular growth. Vitamin D deficiency is associated with blunted intestinal calcium absorption and, together with the tendency for African Americans to

consume less dietary calcium, the attendant reduction in extracellular calcium that doubtless contributes to elevated PTH and may also upregulate expression of inflammatory cytokines while diminishing expression of endothelial nitric oxide synthase (40).

Increased PTH and low vitamin D levels manifested by low plasma 1,25-(OH)2 vitamin D3 as well as reduced intestinal calcium absorption have been observed in the spontaneously hypertensive rat (SHR) model (41). In these respects this animal model is similar to the elevated PTH and vitamin D–deficient state observed for African Americans. Parathyroidectomy attenuated the BP rise in the SHR model (42). Unlike vitamin D–deficient states in other studies, in the SHR model infusion of calcitriol increased vascular tone, intracellular calcium, and long-term exposure, leading to modest increases in BP (43). Resnick *et al.* (12) found 1,25(OH)2D3 to be inversely associated with plasma renin activity in human subjects with essential hypertension demonstrating a similar relationship that has been observed in the VDR knockout mouse model (13). Plasma 25(OH)D3 is also inversely associated with BP in the Dahl salt-sensitive strain of rat, a condition similar to the salt-sensitive hypertension seen in African Americans (44).

Vitamin D, Insulin Resistance, and BP

In African Americans, hypertension has been closely associated with non–insulin- dependent diabetes mellitus (NIDDM), a disorder well known to cause microvascular disease. Epidemiologic data show that hypertension and NIDDM occur at significantly higher rates in African Americans than in Caucasians (45). In fact, these two conditions occur together so often there has been considerable interest in finding a common cellular pathogenetic mechanism. Vitamin D deficiency may be such a connection because there is evidence linking vitamin D, parathyroid hormone, and NIDDM. Hyperparathyroidism has been associated with insulin resistance that can be ameliorated by parathyroidectomy (46), and in a study of uremic subjects, 1,25-dihydroxyvitamin D3 also corrected the insulin resistance and glucose intolerance (47). In this regard also, Chiu *et al.* (48) have demonstrated a significant inverse relationship between serum 25(OH)D3 concentration and insulin sensitivity, suggesting that vitamin D deficiency is associated with pancreatic β cell dysfunction. Mice made diabetic with streptozotocin (STZ) exhibit increased activity of the RAS and hyperglycemia by itself can also stimulate the synthesis of Ang II (49). Endothelial dysfunction has been found early in NIDDM (50) and treatment with large doses of vitamin D has been shown to significantly improve flow-mediated dilation in the brachial artery and to lower BP (51). In addition, activation of the VDR with 1,25(OH)2D3 has been shown to decrease Ang II and inflammatory cytokines in VDR knockout STZ-diabetic mice (49). To the extent these experiments are relevant to human disease, the foregoing suggest upregulation of the RAS and activation of inflammatory cytokines, as described above, may serve as a common mechanism linking vitamin D deficiency, NIDDM, and BP in African Americans. However, at present, the link between vitamin D deficiency, β cell function, and insulin resistance is not well established in African Americans (52,53).

Another important aspect of the association between vitamin D deficiency, insulin resistance, and BP in African Americans relates to the potential effects of vitamin D deficiency on pregnancy, fetal and renal development, and the subsequent development of hypertension. Vitamin D deficiency is associated not only with NIDDM but also with gestational diabetes (54). Studies show a high prevalence of vitamin D deficiency during pregnancy in African American and other women of color that is also associated with lower birth weights and low vitamin D levels in their neonates (55,56). Evidence has accrued from animal studies that hyperglycemia or STZ diabetes occurring during gestation can produce renal dysmorphogenesis, including reduced nephron number that is associated with increased expression of intrarenal angiotensin and NF-κB signaling (57) and may also cause attenuation of arteriolar caliber (58). Thus, vitamin D deficiency may affect intrauterine nephrogenesis and also fetal size and duration of gestation. Because, in humans, reduced nephron number is thought to result from fetal growth retardation, it has been proposed as a possible mechanism for the development of hypertension and renal disease in African Americans (59). Thus, gestational diabetes induced by vitamin D deficiency may have a role, especially because the number of low birth weight children in African Americans is nearly double that of Caucasians. However, at least one study was unable to document reduced nephron number in African Americans (60). Nevertheless, we found that gestational diabetes, rather than gestational age, low birth weight, or fetal growth retardation, contributed significantly to BP in African American children (61). Thus, these data suggest that alterations in renal development and vascular structure and function begin very early in life, most likely, *in utero*, and may be caused by vitamin D deficiency and its secondary effects. These changes are independent of BP and likely set the stage for the future development of hypertension and its subsequent cardiovascular complications.

Caveats

First, the clinical and preclinical data presented here suggest that vitamin D deficiency has a role the development and maintenance of hypertension and the metabolic factors that contribute to it in African Americans and other people of color living away from equatorial regions. However, although it is our contention that this group is at increased risk because of their high prevalence of vitamin D deficiency, there are no data to suggest that Caucasians with vitamin D deficiency would be at lesser risk. Second, although studies have shown VDR activation can ameliorate pathogenetic factors contributing to vascular disease, improvement in BP has not been consistently found (62), raising questions about the effectiveness of vitamin D supplementation and the importance of vitamin D deficiency in hypertension. The reasons for this are several. First, because hypertension is a phenotype, it has many underlying causes, of which vitamin D deficiency is but one. Other hormonal, physiologic, dietary, and clinical factors such as the sympathetic nervous system, dietary sodium, calcium, and potassium intake, and obesity also contribute to BP modulation and vascular tone. Second, the doses or forms of the vitamin D preparations

used in treatment studies may not have been appropriate. Moreover, no treatment study has been directed specifically at African Americans. Third, it may be that, at the time vitamin D supplementation was initiated, vascular changes induced by vitamin D deficiency and subsequent hypertension were no longer reversible. Fourth, VDR polymorphisms have been described that can affect the relationship of blood levels of 25(OH)D3, BP, and target organ damage (63), raising the possibility that such polymorphisms may affect VDR activation and/or its interaction with vitamin D response elements producing variable responses to vitamin D supplementation.

Summary

Despite the above-noted cautions, the body of evidence, accumulated over the last several decades, suggests an important role for vitamin D deficiency in the pathogenesis and maintenance of hypertension in African Americans. We speculate (Fig. 1) that, as a consequence of their displacement from the equator, attenuated cutaneous vitamin D photosynthesis is further diminished, leading to a high prevalence of vitamin D deficiency. This in turn may lead to RAS and inflammatory cytokine activation causing vascular endothelial dysfunction and structural changes to the microvasculature, leading to vascular stiffness and increased resistance, changes that have been shown to precede the onset of hypertension and that also may occur very early in life. Vitamin D deficiency may also play an as yet to be defined role in the genesis and maintenance of salt-sensitive hypertension seen often in African Americans. Through its effects on PTH, pancreatic β cell function, and insulin sensitivity, vitamin D deficiency may contribute to the development of insulin resistance and NIDDM and to gestational diabetes that not only may affect microvascular structure in adults but also may affect fetal growth and retard renal development, thus contributing to the number of functioning nephrons and to vascular changes *in utero*. These changes may predispose also to the development of glomerulosclerosis, thus to fewer functioning nephrons, and together with altered microvasculature may blunt pressure natriuresis, thereby contrib-

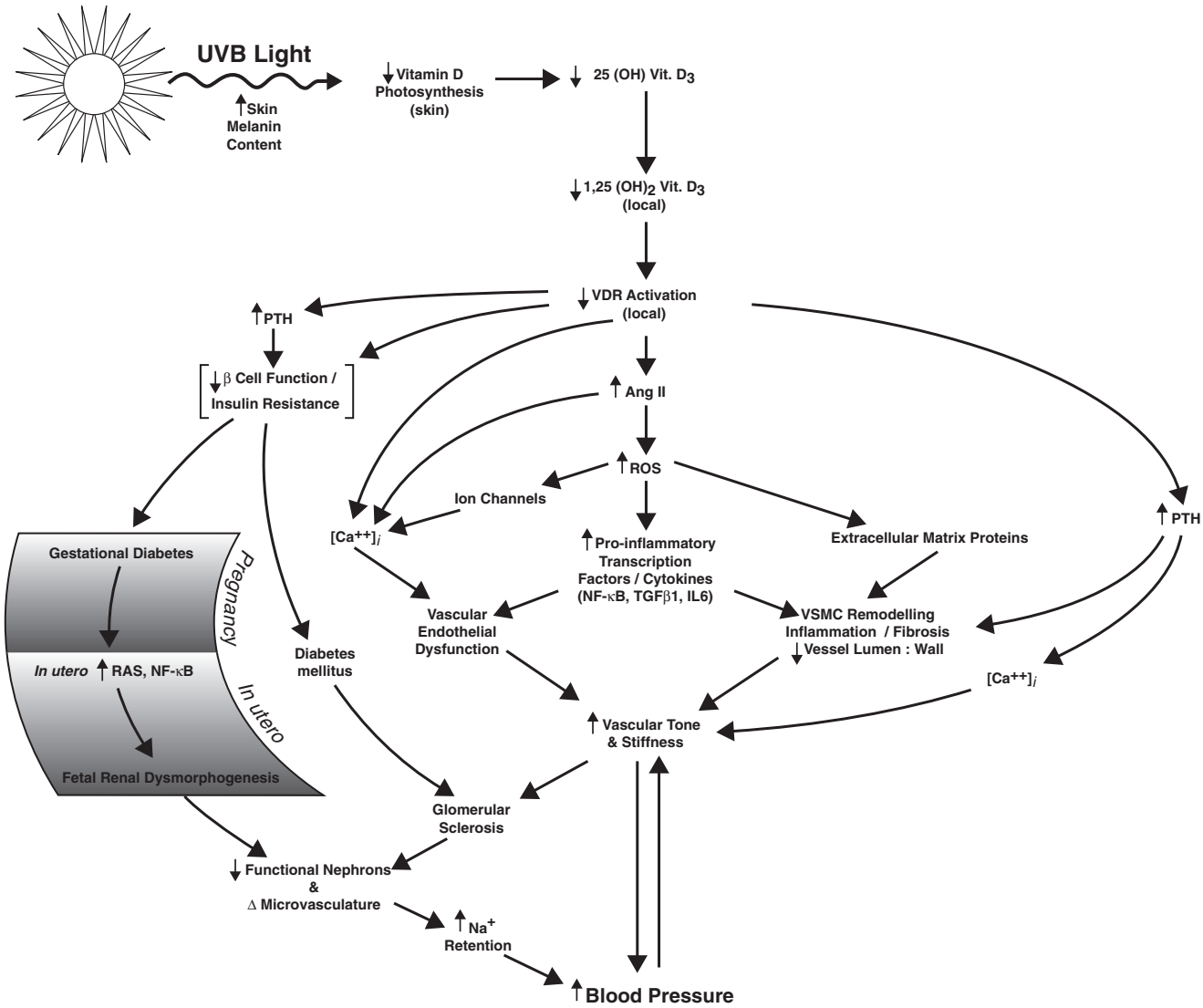

Figure 1. Proposed role for hypovitaminosis D in the genesis and maintenance of elevated BP in African Americans.

uting to sodium retention and salt sensitivity that characterize hypertension in African Americans. Thus, vitamin D deficiency, because of its high prevalence in African Americans beginning at an early age, perhaps even *in utero*, and persisting throughout life may produce changes in large and small arteries and arterioles, creating conditions that may be the basis for the increased risk of African Americans for hypertension and cardio-renal disease. Long-term studies examining the effects of vitamin D supplementation on BP and vascular function in African Americans would be important and are sorely needed.

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