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Differences in RAAS/vitamin D linked to genetics and socioeconomic factors could explain the higher mortality rate in African Americans with COVID-19

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***Abstract*:** COVID-19 is said to be a pandemic that does not distinguish between skin color or ethnic origin. However, data in many parts of the world, especially in the United States, begin to show that there is a sector of society suffering a more significant impact from this pandemic. The Black population is more vulnerable than the White population to infection and death by COVID-19, with hypertension and diabetes mellitus as probable predisposing factors. Over time, multiple disparities have been observed between the health of Black and White populations, associated mainly with socioeconomic inequalities. However, some mechanisms and pathophysiological susceptibilities begin to be elucidated that are related directly to the higher prevalence of multiple diseases in the Black population, including infection and death by COVID-19. Plasma vitamin D levels and evolutionary adaptations of the renin-angiotensin-aldosterone system (RAAS) in Black people differ considerably from those of other races. The role of these factors in the development and progression of hypertension and multiple lung diseases, among them SARS-CoV-2 infection, is well established. In this sense, the present review attempts to elucidate the link between vitamin D and RAAS ethnic disparities and susceptibility to infection and death by COVID-19 in Black people, and suggests possible mechanisms for this susceptibility.

Keywords: African Americans, COVID-19, renin-angiotensin-aldosterone system, vitamin D

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Introduction

Currently, morbidity and mortality rates due to COVID-19 are highest in Black populations in many places around the world. The American Community Survey and Johns Hopkins University have indicated that the infection rate is over 3-fold, and the mortality rate 6-fold, higher in countries with a large Black population than in those with White majorities.[1]

In general, there are marked health disparities between White and African Americans, where the mortality rate of multiple etiologies (cardiovascular and renal disease, diabetes, cancer, and others) for African Americans is significantly higher than for White Americans. Some explanations for such disparities generally include social environment, lifestyle behaviors, socioeconomic status, and access to preventive health care services. Nevertheless, many studies indicate that these factors are not enough to explain such differences. In this sense, it is well established that high vitamin D serum levels have essential benefits on health through multiple mechanisms. African Americans have considerably lower vitamin D serum levels than White Americans. These differences in vitamin D serum concentrations between groups may account for many of the aforementioned health disparities,[2–8] including the susceptibility of Black people to suffering hypertension,

diabetes mellitus, and COVID-19. The latter was recently highlighted by the Wall Street Journal in its article entitled "Vitamin D and Coronavirus Disparities" (https://www.wsj.com/articles/vitamin-d-and-coronavirus-disparities-11587078141). Low vitamin D values are also associated with a higher incidence of respiratory infection.[9] Moreover, in controlled clinical trials, vitamin D administration has shown a protective effect against respiratory infections in healthy patients as well as in patients with chronic obstructive pulmonary disease and other related pathologies, including COVID-19.[10–25]

Additionally, it has been observed that hypertension is an essential risk factor for SARS-CoV-2 infection,[26] and that the renin-angiotensin-aldosterone system (RAAS) is implicated in this process.[27,28] In this regard, it is known that hypertension has a significantly higher prevalence in Black people, possibly because this race presents certain peculiarities compared with the White race.[29] Since the leading causes of death in Black people during slavery were salt-depletive diseases such as vomiting, fevers, and diarrhea, it is argued that African slaves with an improved genetic capacity to conserve salt had a unique survival advantage over the rest. This also allowed them to bequeath their genotype to the next generations of Western Black people. Therefore, it is assumed that, for this reason, African Americans have a higher frequency of subjects with an improved genetic ability to retain salt than African Black people.[30] The sodium retention observed in Black populations causes the inhibition of systemic RAAS (sRAAS) by negative feedback. Thus, decreased renin plasma levels compensate for the tendency to retain salt.[31]

An analogy of the natural sRAAS inhibition observed in Black people is that induced using RAAS inhibitors. In this regard, in the context of the COVID-19 pandemic, the hypothesis has been proposed that RAAS blocker drugs could be a risk factor for patients with SARS-CoV-2 infection since their mechanism of action raises the synthesis of angiotensin-converting enzyme 2 (ACE2) by negative feedback.[32] Indeed, experimental work has demonstrated that the use of these antihypertensive drugs increases ACE2 levels.[33] ACE2 is the receptor to which SARS-CoV-2 binds to enter the cell to cause infection.[34,35]

It has also been suggested that SARS-CoV-2, upon entering the cell through its binding to ACE2 receptors, causes a decrease in intracellular levels of ACE2. ACE2, unlike classical ACE, is responsible for the degradation of angiotensin II. In this way, SARS-CoV-2 would induce the reduction of this protective mechanism of ACE2 on pulmonary parenchyma, worsening the harmful action of angiotensin II on the lungs of patients infected by this virus.[36] As shown in Figure 1, disadvantageous environmental factors, such as social adversity, favor an imbalance between ACE/ACE2.[37–43] This is critical in the African American population due to the lower activity of the ACE2 enzyme, as determined by genetics or epigenetics. This disequilibrium predisposes Black subjects to high blood pressure and cardiovascular risk as well as to lung damage by COVID-19. Additionally, the consequent low levels of angiotensin 1–7 and Mas receptor activation may reduce tissue protection and increase inflammatory response upon a stimulus such as a coronavirus aggression.[36,37] Genetic and epigenetic changes were also detected that seem to correspond to the increased risk among African Americans of developing both diabetes and a greater number of related cardiac, vascular, and renal complications.[44,45] In this context, a controlled interventional study was designed, with high doses of vitamin D in African Americans in an attempt to counteract the described adverse situations. A selected laboratory and genomic response will confirm whether the effect is beneficial.[46]

For these reasons, we suggest that, in addition to disadvantageous socioeconomic and environmental factors present in Black populations, the higher susceptibility of dark-skinned people to infection and mortality by COVID-19 could be influenced by vitamin D deficiency/insufficiency and the particularities of RAAS in this race.

Vitamin D deficiency/insufficiency in dark-skinned people

A study based on the analysis of data from the National Health and Nutrition Examination Survey cycles 2007/2008 through 2013/2014 was performed to describe the prevalence of vitamin D deficiency and insufficiency in adults aged ⩾60 years from the United States (US). In this study, followed by other related studies,[47–55] Black patients showed a higher prevalence of vitamin D deficiency and insufficiency than White patients.

Reduced 25-hydroxyvitamin D serum levels in Black people are related to the increase in skin

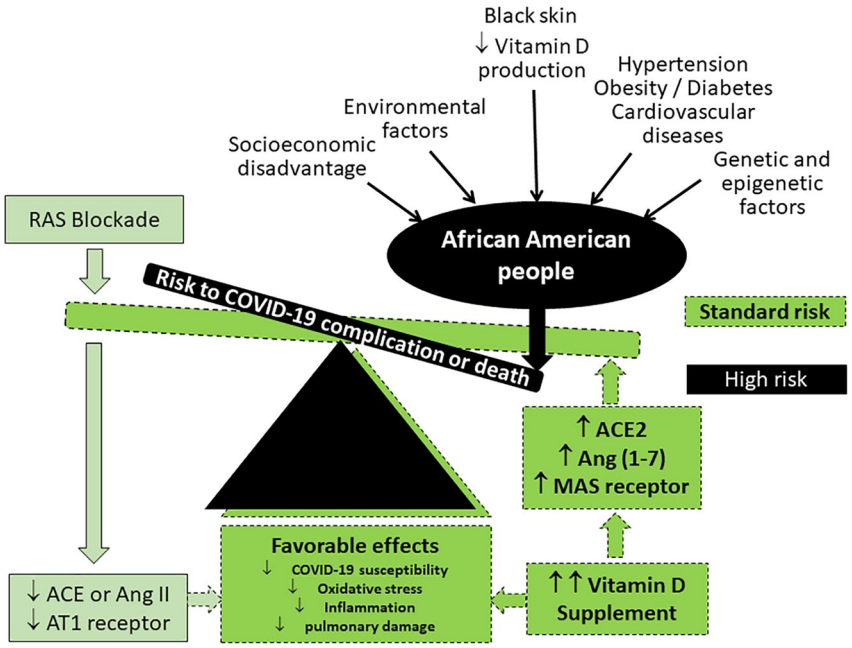

Figure 1. Imbalanced protective and harmful factors related to SARS-CoV-2 infection in African Americans. Multiple genetic and epigenetic factors added to the lack of balance between ACE/ACE2 are critical in the African American population, predisposing it to diseases such as hypertension and diabetes mellitus that worsen the pathophysiology of COVID-19 and increase morbidity and mortality in Black people.
ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2.

pigment and consequent decrease in dermal and hepatic vitamin D3 synthesis.[56–58] People with darker skin need higher doses of ultraviolet B radiation from sunlight than White people to synthesise sufficient amounts of vitamin D.[59,60] In this regard, vitamin D serum levels of a customarily pigmented population were compared with those of an albino Black population in a province of South Africa. Albino children had considerably higher vitamin D levels than normally pigmented children, even though dietary intake and sunlight exposure was similar in both groups. Despite these differences, the parathyroid hormone, plasma and red blood cell magnesium, and plasma calcium levels remained practically unchanged in both groups. This reinforces the idea that the vitamin D deficiency observed in Black people is due mainly to their increased skin pigmentation.[61] A study on infant rickets in North America reported that vitamin D deficiency might occur in children with dark skin, regardless of their social or ethnic origin. Therefore, the administration of vitamin D supplements to children with over pigmented skin whatever their race or economic and social background becomes essential.[62–64] A clinical trial demonstrated that supplementation with 4000 IU/day of vitamin D3 for 1 year in African American men caused the disappearance of any significant difference between their serum levels of 25(OH)D and that of White men.[65,66] Likewise, vitamin D supplementation is especially recommended in obese Black people, since this population group, in particular, has a significant risk of suffering from secondary hyperparathyroidism and vitamin D deficiency.[67,68] In this sense, vitamin D deficiency was compared in obese and non-obese African American children. The obese group had a more significant initial vitamin D deficiency and was even more resistant to treatment with vitamin D3 supplements than the non-obese group.[69] Another study compared vitamin D serum levels of a Norwegian population with an African population (both groups comprised healthy young people and pregnant women). The results showed that, despite the abundant ultraviolet radiation available in the African region studied, vitamin D deficiency was significantly higher in the African population group.[70] Serum levels of vitamin D in winter were measured in a low-income, multiracial elderly population composed of Black, White, and Asian people. The results showed that all groups had

low levels of vitamin D, but the lowest percentage (almost half compared with the other ethnic groups) of vitamin D insufficiency was observed in Black subjects. In contrast, percentages in the White and Asian subsets were very similar between them.[71] It has also been suggested that, although Black people synthesise lower concentrations of vitamin D3 than White people in response to normal sunlight exposure levels in winter and summer, both Black and White populations seem to have a similar ability to absorb and produce vitamin D after repeated exposure to B ultraviolet light at high doses.[72] Although vitamin D synthesis decreases with age in both older Black and White people, the health ABC prospective cohort study showed that mortality was higher in Black than in older White patients, which could be related to the lower vitamin D serum levels found in Black people.[73]

The distinctive vitamin D deficiency observed in Black populations does not seem to affect their bone health (except for the elderly) since their bones are resistant to resorption caused by parathyroid hormone. They also display a superior ability to achieve a more effective renal conservation of calcium than White people. Despite this, vitamin D deficiency may affect many other homeostatic mechanisms, predisposing the Black race to several pathologies.[74–77] It has been observed, for instance, that Black people with tuberculosis have lower serum levels of vitamin D than healthy Black subjects. These circumstances suggest that there may be an association between vitamin D deficiency and susceptibility to pulmonary pathologies.[78,79] A similar situation was observed in young African patients with vitamin D deficiency whose low vitamin D serum level was related to the severity and prevalence of asthma in these patients.[80,81]

The incidence of end-stage renal disease is markedly higher in Black than in White populations, which would be related to the renoprotective effects of vitamin D and its deficiency in dark-skinned people.[82,83] It has been suggested that vitamin D also plays an essential role in the regulation of blood pressure, where deficient concentrations of vitamin D may cause an elevation of blood pressure values. This response would be a possible explanation for the greater susceptibility of Black people to developing hypertension compared with White people.[84] It has also been determined that there is a strong inverse association between C-reactive protein and vitamin D plasma levels. Patients with vitamin D deficiency have higher levels of C-reactive protein, which may influence the development of cancer and multiple cardiovascular diseases (another explanation for the high prevalence of these pathologies in the Black race).[85,86] Additionally, it has been observed that vitamin D deficiency would be related to the development of cardiovascular disease in African American people with type 2 diabetes mellitus. The explanation for this is that vitamin D deficiency would cause downregulation of hydrogen sulfide and cyclic adenosine monophosphate – two crucial signalling molecules related to the prevention of cardiovascular oxidative stress and inflammation. Interestingly enough, this downregulation has not been observed in White diabetic patients. In this sense, *in vitro* studies have shown that vitamin D supplementation increases hydrogen sulfide and cyclic adenosine monophosphate levels. It also contributes to reducing oxidative stress caused by elevated glucose levels, which would be responsible for greater cardiovascular inflammation in African American diabetic subjects. The results suggest that the higher incidence of cardiovascular disease in African American patients compared with White diabetic patients would be a consequence of, among other causes, vitamin D deficiency.[87] Another study has also demonstrated that vitamin D deficiency causes methylation changes in leukocyte DNA, which could induce immune system impairment in patients with vitamin D deficiency.[88] For instance, systemic lupus erythematosus is an autoimmune pathology with a high incidence among African American women. This would also be related to vitamin D deficiency since this vitamin may prevent cellular aging due to telomere shortening, which is a crucial factor in the development and progression of this chronic disease.[89]

Furthermore, another study suggests that skin pigmentation and dietary habits are not the only determining factors in vitamin D deficiency. There is also a genetic association between vitamin D status and the degree of African ancestry of the studied population, since serum concentrations of vitamin D were correlated inversely with high, medium, low, or null African ancestry. Moreover, the effects of diet and sunlight on the rise in vitamin D serum levels were significantly lower in the high African ancestry group than in low/medium ancestry groups.[90] However, vitamin D supplementation may reduce this relationship.[91] The possible ethnic association was

supported by the results of the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) cohort of healthy children and adolescents and the National Health and Nutrition Examination Survey (NHANES), which compared children from different ethnic groups to assess the influence of ethnicity on the concentration of multiple biomarkers. The results showed that vitamin D was one of the biomarkers whose serum levels are influenced by ethnicity.[92,93] Vitamin D binding protein (the leading vitamin D carrier protein in plasma) levels are also lower in Black than in White Americans, which suggests that plasma levels of this protein do not affect the bioavailability of vitamin D in Black people. Despite this, the existence of racial differences in common genetic polymorphisms of Vitamin D binding protein may be responsible for lower vitamin D serum levels in Black subjects, since changes in their affinity for vitamin D directly influence its bioavailability.[94]

Collectively, it is clear that there is a close relationship between vitamin D deficiency (due to either genetic, ethnic, or phenotypic causes) and the prevalence of morbidity and mortality in many pathologies, such as COVID-19 in Black people.

Peculiarities of RAAS in Black populations

African Americans have significantly higher rates of hypertension and related diseases, with Black hypertensive patients being less responsive to treatment with RAAS inhibitors than White hypertensive patients.[95,96] Changes in plasma renin activity, angiotensin II, and aldosterone levels were studied in White and Black hypertensive patients undergoing a high-salt diet followed by a low-salt diet. It was observed that the increase in all plasma components of RAAS after the reduction in salt intake was significantly higher in White than in Black patients, suggesting a less responsive sRAAS in Black patients.[97] The lower sRAAS responsiveness in Black people usually causes hypertension treatment in these patients to require the administration of diuretic drugs or calcium channel blockers in a higher percentage of cases than in White hypertensive patients. This is because antihypertensive monotherapy with RAAS blockers does not achieve efficient results.[98]

Black people are usually characterized by having a significantly reduced plasma renin activity compared with White subjects, which cannot be explained by differences in dietary sodium intake between Black and White populations.[99] Hence, it has been proposed that this lower activity could be related to the maintenance of sodium balance, given the higher tendency of Black people to retain this ion as a genetic adaptation for improving sodium conservation in people that initially inhabited semitropical regions where sodium intake was usually low and hard to acquire.[99] A study of the differences in renal plasma flow in healthy Black populations under a high-salt diet has shown an overactivation of renal RAAS but not of sRAAS in Black people. Slight vasoconstriction was observed in response to angiotensin II infusion before the administration of an ACE inhibitor (captopril). Significant renal vasodilation caused by this inhibitor was also observed, in addition to an improvement of vasoconstriction response to angiotensin II infusion after captopril administration. Continuous renal plasma flow under modulation from a low-salt to a high-salt diet was also noted. These observations suggest higher renal concentrations of angiotensin II in these Black patients. The overactivated intrarenal RAAS would also be responsible for the negative feedback to reduce renin plasma levels in Black people.[100] The capacity of the Black race to retain sodium and water through the genetic polymorphisms of the renal tubular epithelial sodium channel would have allowed the survival of African slaves. It is known that a typical biochemical profile in hypertensive Black people is low or high plasma aldosterone levels, low or null plasma angiotensin I and II levels, and low or null renin activity/concentration. Therefore, there are two hypertension phenotypes in Black people: low or null renin and increased aldosterone concentrations (primary aldosteronism) or low levels of both renin and aldosterone (Liddle syndrome).[30,101,102] Following this, by using RAAS equilibrium analysis (a novel, highly precise method of RAAS assessment), lowered systemic levels of angiotensin I and II were observed in Black hypertensive patients compared with White hypertensive patients.[103]

It is worth noting that the elevated sodium reabsorption observed in African American patients with obesity and hypertension was accompanied by functional medullary hypoxia associated with increased solute reabsorption. This suggests an increase in oxidative stress in African Americans that can worsen hypertension, diabetes mellitus, and many other

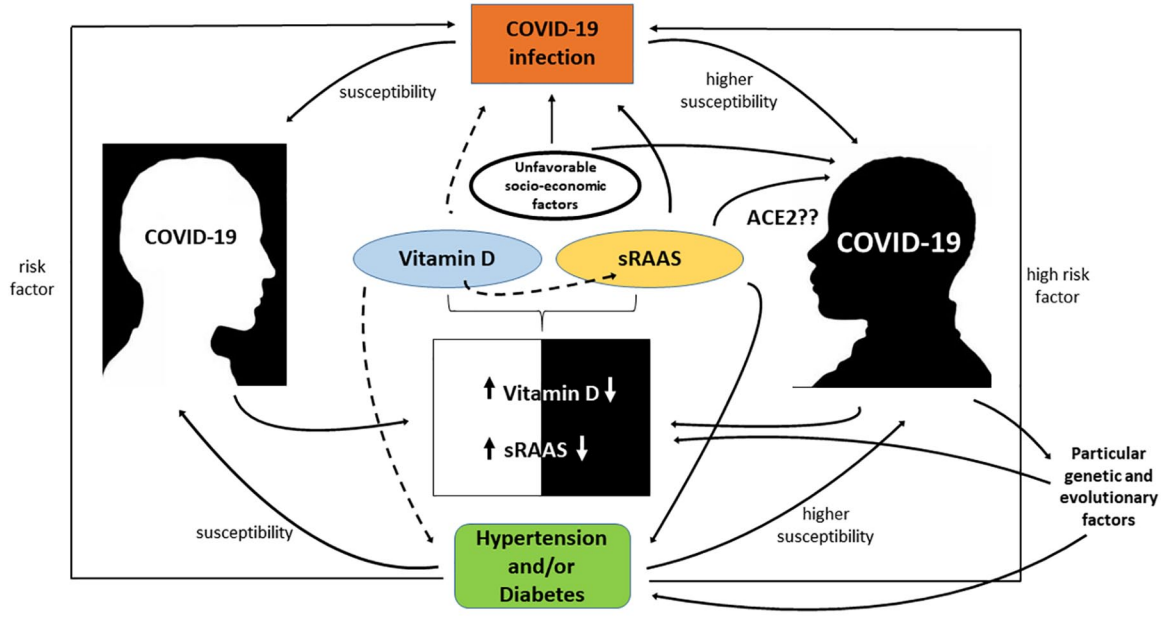

Figure 2. Differential susceptibility to SARS-CoV-2 infection of Black and White populations. Unfavorable socioeconomic factors, low vitamin D levels, and a less-responsive sRAAS impact the susceptibility to infection and death by COVID-19 in Black people. Compared to White people, African Americans have a higher prevalence of hypertension and diabetes mellitus, which are important risk factors for SARS-CoV-2 infection. Dark-skinned, African ancestry level and an increased ability to retain sodium are some of the main genetic and evolutionary factors of this differential ethnic susceptibility. Solid lines indicate stimulation/induction, while dashed lines indicate inhibition/blocking.
ACE2, angiotensin-converting enzyme 2; RAAS, renin-angiotensin-aldosterone system, sRAAS, systemic RAAS.

pathologies (including COVID-19) in comparison with White hypertensive patients.[104]

This evidence would support the idea that, in Black populations, RAAS is inhibited naturally at a systemic level. Therefore, an analogy between this particular behavior and the effect of RAAS inhibitors on ACE2 receptors could be established in COVID-19. However, some studies propose the idea that hypertension in Black people could develop from an imbalance between the RAAS (ACE/Ang II/AT1 receptor) pressor arm and the depressor axis [ACE2/Ang-(1-7)/Mas receptor], where ACE2 as protective RAAS axis would be reduced in hypertensive Black patients.[105] Moreover, another study reported that ACE2 expression was increased only in Asians but not in other ethnic populations.[106] Concerning genetic polymorphisms, African American people have an insertion/deletion polymorphism in the angiotensin I converting enzyme gene, which stimulates higher production of tissue angiotensin II and would predispose them to the development of hypertension and related diseases more frequently than White people.[107]

Moreover, the frequency of the T235 allele of the angiotensinogen gene and the angiotensinogen level was found to be more significant in Black than in White individuals. This racial RAAS disparity would also contribute to the differences in blood pressure levels between White and Black subjects.[108,109] It has also been suggested that the (–535)T allele of angiotensin II type 1 receptor and (–344)T allele of aldosterone synthase can increase the risk of developing hypertension in African Americans but not in Latinos.[110]

Therefore, how RAAS influences mechanisms of susceptibility of Black populations to infection and death by COVID-19 remains unclear. For this reason, more studies should be performed to confirm the proposed hypotheses.

Conclusions and perspectives

Figure 2 summarizes our conceptual explanation of why African American people have the abovementioned susceptibility in the current pandemic. Either due to African genetic ancestry

or phenotypic features of the Black race – such as increased skin pigmentation – and the vitamin D deficiency/insufficiency prevalent in Black people, there is greater susceptibility in this ethnic group to infection and death due to SARS-CoV-2 infection. As a consequence, it is of vital importance to encourage vitamin D intake in the Black population, not only through the diet but also through nutritional supplements. Moreover, it would be necessary to carefully analyze and adjust current vitamin D recommendations since they have been determined assuming there are no disparities between vitamin D requirements in White people and other racial/ethnic groups. In this sense, Rusińska *et al.* have made specific recommendations for people with a dark complexion.[111]

Regarding its peculiarities in the Black race, RAAS could participate in the higher prevalence of infection and death by SARS-CoV-2 in this population. The specific mechanisms involved, however, remain unclear. The expression level of human ACE2 in different tissues, especially in the lungs, may be crucial for the susceptibility to, development, symptoms, and progression of COVID-19. The lower responsiveness of the RAAS in Black people could be related to this, although data are conflicting and this hypothesis is yet to be confirmed.

Author contributions

All authors participated in the conception and design of this review with a substantial contribution to data analysis and interpretation, as well as drafting and critical revision of the article for content and form.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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