

## REVIEW

# Vitamin D and COVID-19: Role of ACE2, age, gender, and ethnicity

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**Abstract**

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, disproportionately targets older people, particularly men, ethnic minorities, and individuals with underlying diseases such as compromised immune system, cardiovascular disease, and diabetes. The discrepancy in COVID-19 incidence and severity is multifaceted and likely involves biological, social, as well as nutritional status. Vitamin D deficiency, notably common in Black and Brown people and elderly, is associated with an increased susceptibility to many of the diseases comorbid with COVID-19. Vitamin D deficiency can cause over-activation of the pulmonary renin-angiotensin system (RAS) leading to the respiratory syndrome. RAS is regulated in part at least by angiotensin-converting enzyme 2 (ACE2), which also acts as a primary receptor for SARS-CoV-2 entry into the cells. Hence, vitamin D deficiency can exacerbate COVID-19, via its effects on ACE2. In this review we focus on influence of age, gender, and ethnicity on vitamin D-ACE2 interaction and susceptibility to COVID-19.

**KEYWORDS**

angiotensin-converting enzyme 2 (ACE2), co-morbidity-COVID-19, cytokine Storm, SARS-CoV-2, vitamin D deficiency

## 1 | INTRODUCTION

### 1.1 | COVID-19 overview

The pandemic initiated in 2019, commonly referred to as (coronavirus disease 2019 [COVID-19]), quickly resulted in a global health crisis that is continuing to date. Although up to 85% of individuals affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are asymptomatic or have mild illness, 15% require oxygen, and 5% require intensive care unit (ICU) admission.<sup>1</sup> The differences in the incidence and severity of COVID-19 are likely to be multifaceted, depending on various biological (such as age, gender, and ethnicity), social (smoking status, co-morbidities),<sup>2</sup> and nutritional factors (e.g., vitamin and nutrient deficiency).<sup>3,4</sup> Understanding these risk factors is essential in providing further protection in such vulnerable populations. It is of importance to note

that there also exist significant interactions among these factors (e.g., aging, gender, and ethnicity).

It is now believed that dysregulated renin-angiotensin system (RAS) pathway is directly related to COVID-19 morbidity and mortality.<sup>5</sup> In fact, angiotensin-converting enzyme 2 (ACE2) receptor, which is an integral part of the RAS pathway, has been established as the functional host receptor for SARS-CoV-2 entry into the alveolar cells.<sup>6</sup> This receptor is also used by SARS-CoV virus, which is responsible for acute respiratory distress syndrome (ARDS).<sup>7</sup> In addition to dysregulated RAS pathway, a variety of other mechanisms including cytokine storm, neutrophil activation, and increased micro-coagulation, might contribute to COVID-19 complications.<sup>8</sup> Interestingly, all these other mechanisms are also affected by RAS. Thus, dysregulated RAS system may at least partially be responsible for the cytokine storm,<sup>9</sup> neutrophil activation,<sup>10</sup> and thrombotic complications.<sup>11</sup> However, central to this discussion is that ARDS may be

aggravated by vitamin D deficiency and tapered down by activation of the vitamin D receptor (VDR).<sup>3,12</sup> Moreover, it has been shown that people of Black, Asian, and minority ethnic (BAME) backgrounds are at a higher risk of developing more severe symptoms than Caucasians, possibly due to vitamin D deficiency.<sup>13</sup>

Early on, it was suggested that countries that lie above 35° north latitude have a relatively higher COVID-19 mortality rate (e.g., 0.6% of patients in southern latitude vs. 14.6% of patients in northern latitude),<sup>14</sup> due to the possibility that at latitude over 35° north, people do not receive sufficient sunlight to retain adequate vitamin D levels during winter.<sup>3</sup> However, more recent data appearing in "Reported Cases and Deaths by Country or Territory" by the United Nations Geoscheme,<sup>15,16</sup> does not support the latitude correlation with COVID-19 risk. In fact, it has been argued that the discrepancy may be due to the higher prevalence of elderly populations in European countries (above 35° North).<sup>17</sup> In addition to age and ethnicity, gender/sex may also be a factor in this equation as it appears that men account for the majority of the severely ill and fatal outcome in COVID-19 compared with women, although men are only slightly more likely than women to be infected.<sup>2,18</sup> Hence, in this review, following a brief discussion on association of age, gender, and ethnicity with COVID-19 outcome we will be focusing on mechanistic interaction of vitamin D with all these factors, primarily through ACE2.

## 1.2 | Angiotensin-converting enzyme 2 (ACE2)

ACE2 is identified as a functional receptor for both coronavirus (CoV) that causes the severe acute respiratory syndrome (SARS)<sup>19</sup> and now SARS-CoV-2 that causes COVID-19.<sup>6</sup> It is hypothesized that the ACE2 gene constitutes a genetic risk factor for SARS-CoV-2 infection.<sup>20</sup> In this regard, ACE2 variants previously reported to be associated with disorders such as hypertension and other cardiovascular diseases, may also be responsible for response variations to COVID-19.<sup>21,22</sup> Indeed, the possible role of genetic variants, gene expression, and epigenetic factors associated with ACE2 in the pathophysiology of COVID-19 has been suggested.<sup>23</sup>

ACE2, is an important regulator of the RAS.<sup>24</sup> ACE2 receptor is part of the dual RAS system consisting of ACE-Ang-II-AT<sub>1</sub>R axis and ACE-2-Ang-(1-7)-Mas axis. The activated ACE-Ang-II-AT<sub>1</sub>R axis may lead to a myriad of health issues including pro-inflammatory and pro-fibrotic effects in respiratory system, vascular dysfunction, myocardial fibrosis, nephropathy as well as defects in insulin secretion, and increased insulin resistance.<sup>25,26</sup> It is hypothesized that SARS-CoV-2 infection down-regulates ACE2 activity, resulting in toxic Ang II accumulation which in turn may cause ARDS or fulminant myocarditis.<sup>27</sup> Activation of the ACE-2-Ang-(1-7)-Mas axis, on the other hand, has anti-inflammatory, anti-fibrotic, anti-antioxidative stress as well as protective effects on vascular function, myocardial fibrosis, nephropathy, pancreatitis, and insulin resistance.<sup>26,28</sup> Thus, the balance between these two axes, which may be influenced by age, sex, and ethnicity as well as body mass index (BMI) can affect the response to COVID-19.<sup>2</sup>

Interestingly, it was recently suggested that metformin, a drug used in diabetes, may specifically be helpful in co-morbid diabetes-COVID-19 conditions, not only due to its effect in lowering the blood sugar level but also because of its enhancement of ACE2 expression leading to cardiopulmonary protection.<sup>29,30</sup>

## 1.3 | Aging and COVID-19

As an emerging infectious disease, the whole population is broadly vulnerable to COVID-19. Early in the SARS-CoV-2 outbreak, it was noted that older adults accounted for a disproportionate number of severe cases and deaths due to COVID-19<sup>31</sup> and this has been corroborated by a number of epidemiological and observational studies.<sup>32</sup> The majority of patients are 50 years of age or older<sup>2,4</sup> and fewer than 1% of patients are under 10 years of age.<sup>33</sup> Advanced age is now considered the principal risk factor for COVID-19 complications. It has been speculated that immune-senescence is a key determinant of outcome in SARS-CoV-2 infections.<sup>32</sup> Therefore, it is not surprising that elderly people with underlying disorders such as hypertension and other cardiovascular diseases, asthma, diabetes, and immune deficiency are at the highest risk of morbidity due to COVID-19.<sup>1,2,4,34</sup>

It has been suggested that the disproportionate SARS-CoV-2 mortality suffered by elderly is due largely to well-recognized features of aging such as: the presence of subclinical systemic inflammation without overt disease, a blunted acquired immune system and chronic inflammation, downregulation of ACE2, and accelerated biological aging.<sup>35</sup> Immunosenescence, entailing changes that occur in both innate and adaptive immunity with aging, is a low-grade inflammatory state triggered by continuous antigenic stimulation and is considered also an important contributor to underlying conditions associated with aging.<sup>36</sup> Specifically, reduction of mitochondrial DNA (mtDNA) and telomeric DNA (telDNA) modulation of systemic inflammation and progressive depletion of telDNA reservoir during aging, are considered as main players in immunosenescence.<sup>37</sup> Interestingly, telDNA reservoir is even lower in aged men compared with aged women, which may also be a contributory factor to gender disparity in response to COVID-19,<sup>37</sup> and discussed further below.

In addition, the thymus, a specialized primary lymphoid organ, within which thymus cell lymphocytes or T cells mature and are critical to the adaptive immune system, could also be a crucial player in the modulation of the immune response toward SARS-CoV-2. Indeed, it has been suggested that reduction in thymopoiesis and thymic output observed after age 40 may at least partially be responsible for COVID-19 severity observed in patients beyond this age.<sup>38</sup> This contention is further supported by the observation that the absence of thymopoietic mechanisms could be associated with cytokine storm, most often reported in adult COVID-19 subjects, especially in the older COVID-19 patients.<sup>39</sup> Cytokine storm occurs as a result of an exaggerated increase in the immune response to a pathogen such as SARS-CoV-2 infection, and appears to be a major player in COVID-19 morbidity and mortality.<sup>40,41</sup>

It is noteworthy that immune senescence, occurs in a complex context, where the aging immune system interacts with an aging body that is undergoing complex metabolic reshaping and remodeling, resulting in a limited capacity of the elderly to fight infection.<sup>42,43</sup> Thus, it appears that failure to trigger an effective adaptive immune response may explain why the elderly cannot optimally control viral replication, leading to endothelial injury, cytokine storm, and disseminated organ injury.<sup>44</sup>

#### 1.4 | Gender/sex and COVID-19

Although the terms “gender” and “sex” are distinct, they are used interchangeably, and we continue the same indifference here. In general terms, “sex” refers to the biological differences between males and females, such as the reproductive organs and genetic differences, whereas “gender” refers to the socially constructed identities and behavior of men, women, or gender diverse people.

It is known that females have increased resistance to viral, bacterial, fungal, and parasitic organisms than males<sup>45</sup> and less susceptibility to microbial infections due to a higher innate immune response than males.<sup>46</sup> For example, women express higher levels of interferon-gamma (IFN- $\gamma$ ), lymphotoxin b (LTb), granzyme A (GZMA), interleukin-12 receptor b2 (IL12Rb2), and granulysin (GNLY) and are less likely to produce extreme immune responses to bacterial or viral infections than men.<sup>46</sup> On the other hand, male patients have higher circulating levels of TNF- $\alpha$  than female patients, which correlates with a worse sepsis prognosis.<sup>47</sup> The protection of females against microbial and viral affections is attributed to the protection provided by the X chromosome and sex hormones, which modulate innate and adaptive immunity.<sup>45</sup>

Differences in male and female susceptibility and response to viral infections lead to gender/sex-dependent differences in incidence and disease severity.<sup>48</sup> Previous clinical studies have shown that women are less susceptible to acquire viral infections and have a reduced cytokine production and that female patient tend to have a higher macrophage and neutrophil activity as well as antibody production and response.<sup>49</sup> For infectious diseases caused by viruses, there are numerous and diverse ways in which sex/gender can impact differential susceptibility between males and females. Although many studies have addressed the sex/gender discrepancy in COVID-19, very few reports have analyzed the underlying cause of gender disparity in COVID-19.<sup>50,51</sup>

Based on an early meta-analysis of 77,932 patients, it was concluded that the morbidity, severity, and mortality of males due to COVID-19 were significantly higher than those of females.<sup>18</sup> The first cases of COVID-19 that occurred in China indicated the presence of gender differences and later studies indicated that men were over two times more likely to die from COVID-19 than women.<sup>34</sup> Another study examining 799 patients in the Tongji Hospital in Wuhan, China found that of 113 COVID-19 deaths, 73% were male and 27% were female.<sup>51</sup> However, the authors hypothesized that this discrepancy could be due to an increased prevalence

of cardiopulmonary disease and smoking in men.<sup>51</sup> A more recent report from the Global Health 50/50 research initiative's sex-disaggregated data consisting of several countries also indicates an increased fatality in men due to COVID-19.<sup>52</sup>

As the COVID-19 pandemic spreads, the differences between male and female mortality and infectivity remain an area of active investigation. The current literature suggests that men tend to have a higher risk of severe infection and mortality related to COVID-19. It is believed that elevated estrogen levels in women may reduce the severity and mortality of COVID-19 deaths through an elevation in the innate and humoral response.<sup>53</sup>

#### 1.5 | Ethnicity and COVID-19

Ethnicity is a complex epidemiological entity made up of genetic, social, cultural, and behavioral patterns. Although ethnicity considerations in COVID-19 are lacking, there is consistent evidence of greater infection rates amongst ethnic minorities.<sup>54</sup> For example, disparities in healthcare access and socioeconomic status, as well as higher levels of medical co-morbidities, are believed to be responsible for the increased risk of contracting COVID-19 in certain ethnic groups.<sup>55</sup> Furthermore, data from the Centers for Disease Control (CDC) suggests that ethnic differences may influence susceptibility and mortality between COVID-19 patients.<sup>56</sup> For instance, even though African American constitute only 13% of the US population, 33% of hospitalized COVID-19 patients consisted of this ethnic minority. However, the higher incidence of co-morbid conditions in this ethnicity adds a layer of complication to interaction between ethnicity and COVID-19.<sup>54,55</sup> In this regard, underlying conditions such as diabetes can significantly contribute to adverse outcome to COVID-19. Currently, both diabetes and COVID-19 are considered worldwide pandemics with similar risk factors such as obesity, nonwhite ethnicity, and poorer socioeconomic status.<sup>30</sup>

In addition to co-morbid conditions, several other factors may contribute to certain ethnic group vulnerability. Thus, it is speculated that globalization due to the interaction of individuals from diverse migrant and ethnic backgrounds plays a role. For example, co-habiting in intergenerational familial units, differences in educational background, professional roles, socioeconomic status, and health-seeking behaviors are different in Black, Asian, and other ethnic communities compared to the White population, which can influence the risk and response to infectious diseases.<sup>57</sup> However, further studies on mechanisms that may contribute to increased risk of COVID-19 morbidity and mortality in ethnic minority communities are necessary.

#### 1.6 | Aging and ACE2

Mortality due to COVID-19 is highly associated with advanced age, owing in large part to severe respiratory tract infection. Whether ACE2 level in the lung specifically contributes to age-associated

vulnerability is currently unknown. Typically, ACE2 expression decreases with age in both sexes. However, as indicated above, men have a more significant age-dependent decrease in ACE2 compared with women.<sup>58</sup> Interestingly, a similar scenario is observed in rats. Thus, the level of ACE2 is dramatically reduced with aging in both sexes, but this reduction is significantly higher in aged male compared with female rats.<sup>59</sup>

Compared with young individuals, older persons, particularly those with cardiovascular disease have reduced ACE2 levels and hence are more predisposed to exaggerated inflammation, which by itself can further reduce ACE2 expression, leading to a vicious cycle in the context of COVID-19.<sup>60</sup>

Some studies suggest that child-specific plasma ACE2 profile may be the reason behind the discrepancy in COVID-19 infection between the young and the old. Moreover, children usually have higher plasma ACE2 levels than adults.<sup>61</sup> For example, ACE2 plasma levels in children (6 months to 17 years of age) were 13–100 U/L compared with 9–67 U/L in the adult population.<sup>62</sup> This decrease of ACE2 with age seems to parallel the increase in COVID-19 mortality in the aged population. Interestingly, the two host receptors that have been proposed for COVID-19 virus, CD26 and ACE2, are both associated with senescence.<sup>63</sup>

## 1.7 | Gender and ACE2

There is increasing evidence that sex and sex hormones affect many components of the circulating as well as tissue-based RAS including ACE2.<sup>64–66</sup> More recently, it was shown that estrogen modulates the local RAS in human atrial myocardium via downregulation of ACE and simultaneous upregulation of ACE2, angiotensin II receptor 2 (AT2R), and MAS expression levels.<sup>67</sup> The ACE2/Ang1-7/Mas receptor axis appears to be of greater relevance in women than in men.<sup>67</sup> ACE2 expression not only varies between males and females, but also by age. Hence, elderly men have a more significant decrease in ACE-2 compared with elderly women.<sup>58</sup> A decrease in ACE2 expression/activity may lead to sustained ACE-mediated generation of Ang-II and downstream signaling deleterious to organ functions including that of lung, kidney, and heart.<sup>68</sup> Thus, hormonal and genetic factors could lead to ACE2 overexpression in females, accounting at least partially for the better outcome and lower death rate in female SARS-CoV-2 patients. However, it remains to be determined whether indeed the expression of ACE2 differs in the lungs of male or female patients.<sup>49</sup>

## 1.8 | Ethnicity and ACE2

Studies show that genetics along with other risk factors can determine an individual's susceptibility to respiratory tract infections.<sup>69</sup> Since ACE2 receptor on host cells acts as an entry point for SARS-CoV-2,<sup>70</sup> it has been hypothesized that the ACE2 gene constitutes a genetic risk factor for SARS-CoV-2 infection.<sup>20</sup> Variations in

immunity and ACE2 expression may lead to specific vulnerability and intensity of SARS-CoV-2 infection.<sup>58</sup> ACE2 variants were previously reported to be associated with disorders such as hypertension and other cardiovascular diseases.<sup>21</sup> These diseases are often comorbid with COVID-19 and may pose promising genetic factor candidates for COVID-19 susceptibility. Moreover, variation in the expression of ACE2 and associated epigenetic factors may play a significant role in determining an individual's or ethnic susceptibility to COVID-19.<sup>23</sup>

ACE2 expression differs between the world's three main racial groups: Africans, Asians, and Caucasians,<sup>2</sup> where Asians have significantly higher ACE2 expression in various organs, but not in the lung compared to the other two ethnic groups.<sup>2,50,70</sup> Interestingly, there was also a gender-dependent site variation in the ACE2 levels of the Caucasian group, signifying interactions between aging and ethnicity. Whereas age-dependent decrease in ACE2 expression was observed in the blood, colon, adrenal gland, nerves, adipose tissue, and salivary glands of the males, such observation was absent in nerves, adipose tissue, or saliva of the females.<sup>2</sup>

Studies focusing on the Black population, show a reduced molecular expression of ACE2 compared with other races. Reduced plasma levels of ACE2 are also observed within populations of African descent including, African Americans and more specifically in individuals with pre-hypertensive status, diabetes, and renal disease.<sup>71</sup> This may at least partially explain the reason for the higher predisposition for developing essential arterial hypertension and early end-organ damage in Blacks leading to higher mortality due to COVID-19 in this race.<sup>72,73</sup>

## 1.9 | Vitamin D

Vitamin D is a group of fat-soluble secosteroid (a steroid with a "broken" ring) hormone, produced endogenously from 7-dehydrocholesterol with the help of sunlight or ultraviolet irradiation that is mainly involved in controlling calcium and phosphorus homeostasis. The most important compounds in this group in humans are vitamin D3 or cholecalciferol and vitamin D<sub>2</sub> or ergocalciferol. In the liver, cholecalciferol is converted to calcifediol (25-hydroxycholecalciferol), whereas ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites, called 25-hydroxyvitamin D or 25(OH)D, are measured in serum to determine a person's vitamin D status. A main distinction between the two vitamins is that vitamin D3 comes mainly from food of animal origin, whereas vitamin D<sub>2</sub> comes from fungi. In addition, calcifediol is further hydroxylated by the kidneys to form calcitriol or 1,25-dihydroxycholecalciferol (1,25(OH)<sub>2</sub>D).<sup>74</sup> The primary enzyme responsible for the later reaction is CYP27B1 in the kidneys, although other tissues including various epithelial cells, cells of the immune system, and the parathyroid gland also contain this enzymatic activity.<sup>75</sup> Calcitriol, which is the biologically active form of vitamin D circulates as a hormone in the blood, and by regulating the concentration of calcium and phosphate promotes the healthy growth and remodeling of bone. It also has an effect on cell growth,

neuromuscular and immune functions,<sup>76,77</sup> where the later leads to a reduction of inflammation.<sup>78</sup>

Vitamin D deficiency afflicts almost 50% of the population worldwide and is considered a public health problem affecting not only the elderly but also people across all life stages.<sup>79,80</sup> A majority of healthy individuals have low vitamin D concentration, mainly at the end of the winter due to inadequate sun exposure.<sup>76</sup> In fact, individuals who stay at home or might be night workers may suffer from vitamin D deficiency for the same reason.<sup>81</sup> Vitamin D deficiency is an independent risk factor for total mortality in the general population<sup>82</sup> and is associated with increased susceptibility to respiratory infections.<sup>83</sup> According to Endocrine Society and Society for Adolescent Health and Medicine, the following cut-offs for 25(OH)D with specific designations are adopted to define vitamin D status: deficiency: < 50 nmol/L; insufficiency: 50–75 nmol/L; sufficiency: ≥ 75 nmol/L. Hypovitaminosis D is defined as 25(OH)D levels < 75 nmol/L or (30 ng/mL), and severe vitamin D deficiency is defined as 25(OH)D levels < 25 nmol/L.<sup>15,84</sup>

### 1.10 | Vitamin D and COVID-19

There is now sufficient evidence to indicate that vitamin D deficiency compromises the respiratory immune function and can result in an increased risk of COVID-19 severity and mortality.<sup>85</sup> Indeed, SARS-CoV-2 positivity rate is associated with circulating 25(OH)D levels,<sup>86</sup> and various degrees of vitamin D deficiency are correlated with various degrees of COVID-19 severity and mortality.<sup>87</sup> Moreover, vitamin D may lower the risk of COVID-19 infections and deaths through different mechanisms discussed below. Vitamin D deficiency is also believed to be involved in ARDS, heart failure, and sepsis, all features of critically ill COVID-19 patients.<sup>85,88</sup> Vitamin D deficiency may also be related to geographic variations in incidences of ARDS and COVID-19.<sup>89</sup> Thus, it has been suggested that vitamin D may be used prophylactically to decrease the severity of illness caused by SARS-CoV-2, especially in settings where hypovitaminosis D is common.<sup>5</sup> Vitamin D supplementation may also protect musculoskeletal health in those at risk of deficiency due to being housebound.<sup>14</sup>

The postulated mechanisms involved in vitamin D protection against COVID-19 include interaction with ACE2 (discussed below), suppression of cytokine response as well as maintenance of cell junctions and strengthening cellular immunity.<sup>85</sup> Suppression of cytokine response and reduced severity/risk for ARDS were evident by a meta-analysis where regular oral vitamin D<sub>2</sub>/D<sub>3</sub> intake (in doses up to 2000 IU/day) was found to be safe and protective against acute respiratory tract infection and COVID-19.<sup>5,85</sup> Nonetheless, further research is needed to understand the effects of Vitamin D and the role of various cytokines prevalent in nasal/pharyngeal illnesses on COVID-19 pathogenesis, which may actually lead to novel therapeutic indications.<sup>90</sup>

### 1.11 | Vitamin D and ACE2

Vitamin D is a negative endocrine RAS modulator and inhibits renin expression and generation. It can induce ACE2/Ang-(1-7)/MasR axis activity and inhibit renin and the ACE/Ang II/AT1R axis, thereby increasing the expression and concentration of ACE2, MasR, and Ang-(1-7) and producing a potential protective role against acute lung injury/acute respiratory distress syndrome (ARDS). Vitamin D also helps contain the virus by dampening the entry and replication of SARS-CoV-2 via multiple mechanisms. These mechanisms include: reduction of pro-inflammatory cytokines and increasing anti-inflammatory cytokines, enhancement of natural antimicrobial peptides, and activation of defensive cells such as macrophages that could destroy SARS-CoV-2.<sup>91</sup> More importantly and directly relevant to the subject, vitamin D might alleviate ARDS and acute lung injury induced by SARS-CoV-2 by modulating ACE2.<sup>92</sup> Therefore, targeting the unbalanced RAS and ACE2 downregulation with vitamin D is a potential therapeutic approach to combat COVID-19 and ARDS.<sup>93</sup> Moreover, since angiotensin type 1 receptor (AT1R) antagonists and vitamin D can increase the expression of ACE2 independently, the possibility of repurposing AT1R antagonists and combining it with vitamin D to treat COVID-19, appears as an attractive option.<sup>94</sup>

It was reported earlier that vitamin D administration enhances the level as well the mRNA expression of VDR and ACE2 in a rat model of LPS-induced acute lung injury, suggesting that increased expression of ACE2 and VDR had a role in vitamin D protection against acute lung injury.<sup>95</sup> Thus, clinical features and pathological changes of lung tissues in the calcitriol (a synthetic vitamin D)-treated LPS rats were remarkably milder than controls.<sup>95</sup> It was later confirmed that vitamin D may decrease LPS-induced acute lung injury by inducing ACE2/Ang-(1-7) axis and suppressing renin and the ACE/Ang II/AT1R axis.<sup>96</sup>

Compared with subjects with sufficient 25(OH)D levels (≥30 ng/ml), those with insufficiency (15–29.9 ng/mL) and deficiency (<15 ng/ml) may present with higher circulating Ang II concentrations. Furthermore, those with vitamin D deficiency may have blunted renal plasma flow responses to infused Ang II.<sup>97</sup> Normalization of vitamin D concentrations, however, can lower RAS activity by transcriptional suppression of renin expression and hence restore normal renal flow.<sup>12</sup>

It was also observed that calcitriol decreased ACE concentration and ACE/ACE2 ratio and enhanced ACE2 concentration in diabetic rats. Thus, calcitriol treatment effectively weakened ACE upregulation and ACE2 downregulation in such rats.<sup>98</sup> Interestingly, administration of another synthetic vitamin D analog, paricalcitol, led to increased levels of ACE2 in tubular cells and decreased levels of ACE2 within the circulation, effectively slowing the development of nephropathy in diabetic rats.<sup>99</sup> It was later reported that calcitriol suppresses Ang II receptor type 1 (AT1) and ACE and reduces Ang II formation in the spontaneously hypertensive rats with an eventual elevation of ACE2, MasR, and Ang-(1-7) production.<sup>100</sup>



## 1.12 | Aging, vitamin D and COVID-19

The correlation between COVID-19 severity and age can be explained based on immune decline (immune-senescence) and vitamin D insufficiency. Although there is a complex interplay between vitamin D and various components of the innate and adaptive immune responses to bacterial and viral infections, vitamin D has been found to modulate macrophages' response, preventing the release of inflammatory cytokines and chemokines.<sup>101</sup> As alluded to earlier, COVID-19 is exacerbated by the release of pro-inflammatory cytokines. Thus, patients with common variable immunodeficiency and bronchiectasis,<sup>102</sup> as well as older adults with mild to severe vitamin D deficiency,<sup>103</sup> constitute high-risk groups for succumbing to COVID-19. In addition, patients with cardiovascular diseases, diabetes mellitus, obesity, and smoking, all of which are significant risk factors in COVID-19 and would eventually require ventilatory support may present with vitamin D deficiency.<sup>104</sup> Thus, it has been suggested that vitamin D status may be a surrogate indicator for morbidity and mortality of patients with COVID-19, particularly in the elderly.<sup>105</sup>

## 1.13 | Gender, vitamin D, and COVID-19

COVID-19 has a significantly higher lethality in men than in women (ratios up to 3:1), suggesting the presence of sex-dependent biological factors underlying these differences in disease outcome.<sup>106</sup> It is known that in general, innate and acquired immune responses are more intense in females than in males.<sup>107</sup> This can provide women with a more effective defense to fight new and infective pathogens, favoring viral clearance. Another significant explanation for sex differences in COVID-19 lethality is the sex-dependent modulation of cellular receptors and co-receptors used by SARS-CoV-2 to enter human host cells. In particular, ACE2 is encoded on X-chromosome in sites commonly escaping the inactivation of one X-chromosome in mammalian XX cells and could therefore be overexpressed in women.<sup>108</sup> Moreover, estrogen induces an increase of ACE2 expression that, as reported above, could play a protective role in acute respiratory distress.<sup>67</sup> On the other hand, androgen can increase the expression and activation of transmembrane serine-protease 2, (TMPRSS2), which facilitates virus-cell membrane fusion, thus favoring the infection.<sup>109</sup>

A large number of patients with COVID-19 exhibit severe cardiovascular damage and those with pre-existing cardiovascular diseases appear to have an increased risk of death.<sup>110</sup> Estrogen has known protective effects on the cardiovascular system mediated by estrogen receptors, resulting in the activation of endothelial nitric oxide synthase. Moreover, estrogen modulates serum lipoprotein and triglyceride levels and influences the expression of coagulant and fibrinolytic proteins. These estrogen-mediated actions could represent a further reason for the sex-specific differences in the outcome of COVID-19.<sup>111</sup>

Sex differences have also been observed in the immunomodulatory and anti-inflammatory effects of vitamin D in some autoimmune diseases. In particular, it was reported that vitamin D induces a stronger inhibition of the production of pro-inflammatory cytokines and a higher increase of anti-inflammatory cytokines in lymphocytes of female patients afflicted with multiple sclerosis in comparison with those from male patients.<sup>112</sup> Hence, it was suggested that vitamin D in an estrogen-dependent manner controls T cell differentiation.<sup>113</sup> Moreover, estrogen seems to increase the expression of the nuclear VDR gene in CD4 + T cells and to decrease the expression of CYP24A1, the cytochrome P450 component of the 25-hydroxyvitamin D(3)-24-hydroxylase enzyme which inactivates vitamin D,<sup>114</sup> hence giving an edge to women in combatting COVID-19. However, it is noteworthy that post-menopausal women tend to exhibit vitamin D deficiency.<sup>115</sup>

## 1.14 | Ethnicity, vitamin D, and COVID-19

There are now strong indications that the acquisition, transmission, and severity of COVID-19 might be influenced by ethnicity.<sup>116</sup> Specifically, Black, Asian, and Minority ethnic community may be more susceptible to severe presentations of COVID-19.<sup>117</sup> For example, in Chicago, more than 50% of COVID-19 cases and nearly 70% of COVID-19 deaths involve Black individuals, although Blacks make up only 30% of the population. Similarly, in Louisiana, 70.5% of deaths have occurred among Black persons, who represent 32.2% of the state's population. In Michigan, 33% of COVID-19 cases and 40% of deaths have occurred among Black individuals, who represent 14% of the population. In New York City, Blacks and Hispanics, accounting for 28% and 34% of deaths, respectively, represent 22% and 29% of population, respectively.<sup>118</sup> Moreover, in predominantly Black counties in the United States, the infection rate is more than three-fold higher and death rate is over six-fold higher than in predominantly White counties. Aside from the co-morbid condition, it must be acknowledged that the communities where many Black people reside are in poor areas characterized by high housing density, high crime rates, and poor access to healthy foods. Since low socioeconomic status alone is a risk factor for total mortality independent of any other risk factor, such social determinants of health must be considered in a complex equation, including COVID-19 mortality.<sup>118</sup>

Hypertension has a significantly higher prevalence in Blacks compared with Caucasians,<sup>119</sup> partly, due to lower activity of the ACE2 enzyme in this population.<sup>120</sup> 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.<sup>23,28</sup>

Vitamin D has essential benefits on health through multiple mechanisms including interaction with ACE2. However, African Americans have considerably lower vitamin D serum levels than White Americans. BAME produces less vitamin D as a result of

higher skin melanin content.<sup>121</sup> These differences in vitamin D serum concentrations between groups may account for many of the aforementioned health disparities such as susceptibility of black people to hypertension, diabetes, and COVID-19.<sup>122,123</sup> 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.<sup>124</sup> Nonetheless, additional studies are imperative to gain a better understanding of the interaction of vitamin D with ACE2 and its role in COVID-19.

## 2 | CONCLUSION

In summary, vitamin D deficiency in elderly people, particularly men as well as in select ethnic groups such as Blacks may contribute to higher morbidity and mortality in these populations due to COVID-19. ACE2 may be a common denominator in the susceptibility of these individuals, although further investigation in this regard is warranted. Nonetheless, supplement with vitamin D may be of particular benefit against COVID-19 in select populations where the risk of vitamin D deficiency is high.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Yousef Tizabi and Bruk Getachew conceived and discussed the idea. Bruk Getachew wrote the first draft. Yousef Tizabi provided critical advice and reviewed the manuscript. Both authors approved the final version of the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available as listed in the references.

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