Unraveling the roles of vitamin D status and melanin during COVID-19 (Review)

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Abstract. As the coronavirus disease 2019 (COVID-19) continues to spread worldwide, it has become evident that the morbidity and mortality rates clearly vary across nations. Although several factors may account for this disparity, striking differences within and between populations indicate that ethnicity might impact COVID-19 clinical outcomes, reflecting the ‘color of disease’. Therefore, the role of key biological variables that could interplay with viral spreading and severity indices has attracted increasing attention, particularly among non-Caucasian populations. Although the links between vitamin D status and the incidence and severity of COVID-19 remain elusive, several lines of emerging evidence suggest that vitamin D signaling, targeting several immune-mediated pathways, may offer potential benefits at different stages of SARS-CoV-2 infection. Given that the vitamin D status is modulated by several intrinsic and extrinsic factors, including skin type (pigmentation), melanin polymers may also play a role in variable COVID-19 outcomes among diverse population settings. Moreover, apart from the well-known limiting effects of melanin on the endogenous production of vitamin D, the potential crosstalk between the pigmentary and immune system may also require special attention concerning the current pandemic. The present review article aimed to shed light on a range of mostly overlooked host factors, such as vitamin D status and melanin pigments, that may influence the course and outcome of COVID-19.

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Abbreviations: ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; ARDS, acute respiratory distress syndrome; AT1R, AT1 receptor; BAME, Black, Asian and Minority Ethnic; CoV, coronavirus; COVID-19, coronavirus disease 2019; 7-DHC, 7-dehydrocholesterol; 1,25(OH)2D3, 1,25-dihydroxyvitamin D3; 25(OH)D, 25-hydroxyvitamin D; IFN-γ, interferon-γ; MasR, Mas receptor; NF-κB, nuclear factor-κB; RAS, renin-angiotensin system; ROS, reactive oxygen species; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th, T helper; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; Tregs, regulatory T cells; UV, ultraviolet; UVR, ultraviolet radiation; VDR, vitamin D receptor

Key words: coronavirus disease 2019, viral infection, skin pigmentation; immune response, immunity, ethnicity

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1. Introduction

Since the beginning of the 21st century, the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV) has marked the third large-scale epidemic of a highly pathogenic coronavirus (CoV) in the human
population, following SARS-CoV in 2002 and the ongoing Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (1,2). Coronavirus disease 2019 (COVID-19), an acute respiratory disease, has rapidly spread beyond its Chinese epicenter in Wuhan since late 2019, creating a public health burden of international concern.

While the COVID-19 pandemic continues to advance globally, the reports on clinical outcomes and risk factors for morbidity and mortality are increasingly emerging as the virus reaches new geographic areas. Despite the difficulties in cross-country comparisons, COVID-19 cases and mortality rates clearly vary around the globe (3,4). Several factors may account for this discrepancy, including differences in population composition, age distribution, genetic predisposition, general health, healthcare access and socioeconomic status (5,6). Although striking differences in SARS-CoV-2 infection within and between populations indicate that ethnicity may affect disease outcomes (7), little is known of the mechanisms within and between populations. It is thus important to elucidate host factors that may influence susceptibility and/or response to SARS-CoV-2.

In this regard, interest has currently focused on the potential impact of vitamin D status on COVID-19 outcomes (13-15). In fact, it is already evident that the prevalence of vitamin D deficiency in Europe, particularly in the northern mid-latitudes, seems to be closely aligned to increased COVID-19 morbidity and mortality (16,17). Moreover, certain non-white ethnic groups that are at higher risk of severe vitamin D deficiency [Black, Asian, and Minority Ethnic (BAME)] appear to be disproportionately affected by COVID-19 (18,19).

Indeed, recent research has indicated that vitamin D signaling, mediating several antiviral and immune-enhancing pathways, may exert beneficial effects at different stages of COVID-19. The regulatory role of vitamin D in immune cell function, particularly by maintaining a dynamic balance between pro- and anti-inflammatory cytokine signals through modulating effects on the renin-angiotensin system (RAS), seems to be of particular importance in the context of severe COVID-19. Thus, although vitamin D deficiency may increase the risk of upper respiratory viral infections, it is the impact of the vitamin D status on cytokine profiles that is potentially much more relevant to the pathogenesis of COVID-19, pointing to a higher inflammatory response (‘cytokine storm’) in vitamin D-deficient individuals if exposed to SARS-CoV-2 (13-15,17,20).

Given the supportive role of vitamin D in immune responses against respiratory viruses (21), these observations require particular attention. Since vitamin D mainly results from endogenous skin production following exposure to ultraviolet (UV) solar radiation (22), skin pigmentation may require particular attention. Since vitamin D mainly results from endogenous skin production following exposure to ultraviolet (UV) solar radiation (22), skin pigmentation may thus play a role in non-white ethnic variations of COVID-19, as melanin can reduce the capacity of the skin to effectively absorb sunlight and synthesize vitamin D3. The present review article aimed to explore the evidence related to vitamin D status and melanin pigmentation that may have clinical implications on the course and outcomes of COVID-19.

2. SARS-CoV-2 infection

SARS-CoV-2 is an enveloped, positive-sense, and single-stranded RNA β-coronavirus that spreads mainly through the respiratory tract by exploiting the angiotensin-converting enzyme 2 (ACE2) as an entry receptor to infect lung alveolar and intestinal epithelial cells (1,23). The initial binding between SARS-CoV-2 Spike (S) glycoprotein and ACE2 receptor on the surface of target cells is thus a critical step for virus entry, determining the virus-host range and cellular tropism, as well as the virus-cell membrane fusion. ACE2, found in abundance in the human respiratory tract, has therefore taken center stage in the COVID-19 outbreak, as it can regulate both the cross-species and human-to-human transmission of SARS-CoV-2 (1).

The clinical spectrum of COVID-19 disease has been well documented. Infection with SARS-CoV-2 seems to follow a strikingly divergent course, ranging from non-symptomatic to life-threatening: The majority (80-85%) of patients affected remain asymptomatic or display mild flu-like symptoms, while the remaining 15% develop severe disease and 5% of cases progress to a critical condition, with deaths mainly occurring in older and chronically ill patients as a result of acute respiratory distress syndrome (ARDS), sepsis and multiorgan failure (24,25).

Of note, recent observational data have demonstrated an unusual risk factor pattern. While arterial hypertension and diabetes mellitus are the most commonly reported risk factors for more severe outcomes, patients with underlying lung conditions, i.e., chronic obstructive pulmonary disease, seem to be relatively protected from severe forms of COVID-19 (26). In addition, unlike influenza, a mild clinical course in the pediatric population has already been described. Curiously, the latter two groups are generally considered more vulnerable to respiratory pathogens (15,26).

Although the immune response is vital for the control and resolution of SARS-CoV-2 infection (1), virus-host interactions trigger a diverse set of immune mediators against the invading virus, which is followed by immune overreaction and induction of a cytokine storm (excessive cytokine release) in at-risk individuals, as a known pathogenic event of ARDS development (1,16). In this context, the RAS cascade has emerged at the forefront of COVID-19 pathophysiological mechanisms, although angiotensin II (Ang II) has been more well known for its cardiovascular and renal functions. Considering the ACE2 targeting by SARS-CoV-2, the RAS imbalance has been proposed to play a pivotal role in the pathogenesis of COVID-19. This hypothesis is mainly based on the reduction of transmembrane ACE2 as a result of enzyme endocytosis along with the S-glycoprotein of the virus. The consequent over-stimulation of the classical ACE/Ang II/AT1 receptor (AT1R) axis in line with the downregulation of the anti-inflammatory ACE2/Ang-(1-7)/Mas Receptor (MasR) arm can compromise the depressor/pressor balance of RAS, resulting in a hyper-inflammatory state that may partially be responsible for the severe complications associated with COVID-19 (26).

3. COVID-19 in skin of color

As the pandemic continues to spread worldwide, it has become evident that individuals of different ethnic backgrounds, but
sharing a BAME origin appear to be more severely affected by COVID-19 compared to Caucasians (19). Increasing numbers of reports have demonstrated a pattern of higher risk for infection and adverse clinical outcomes from COVID-19 in ethnic minority groups (7,27-30). Recent UK data have revealed that over one-third of COVID-19 confirmed cases admitted to intensive care are of a BAME background (7). In addition, based on the UK Biobank data (2006-2010), both all-cause and COVID-19-related mortality rates have been estimated to be higher among ethnic minorities compared to the Caucasian British population during the first pandemic wave (19). Similarly, increased incidence and severity among African-American and minority communities have also been documented in the United States (31).

While the reason behind these disparities is probably multifactorial, involving a lower socioeconomic or medical comorbidity status, the disproportionate effect of COVID-19 on certain ethnic groups requires special attention. Although ethnicity may interplay with SARS-CoV-2 morbidity and mortality through different cultural, behavioral and social traits (7), exploring the mechanisms underlying the association between genetic variability and COVID-19 outcomes is obviously warranted by the evidence (5,19).

Currently available data suggest that vitamin D deficiency may represent a potential mediator for poor COVID-19 outcomes in people of color (18). Given that highly melanized skin has long been shown to attenuate the cutaneous biosynthesis of vitamin D (32), indeed, key biological variables, including melanin, that may impact these observations should be considered.

### 4. Potential role of melanin in the era of COVID-19

Melanin pigments are considered the main drivers of human pigmentation status (33). Two types of melanin, i.e., eumelanin (brown/black) and pheomelanin (red/yellow) polymer, are produced within specific organelles (melanosomes) in epidermal melanocytes and are then transported into the surrounding keratinocytes. Specialized melanocytic enzymes and proteins are involved in melanin biosynthesis, with tyrosinase being the key enzyme catalyzing the initial step of melanogenesis, i.e., the oxidation and polymerization of the amino acid tyrosine to form the intermediate dopaquinone (33-35). Skin color diversity across individuals is mainly the result of differences in melanin content; the amounts of melanin in epidermal cells vary depending on the cutaneous phenotype, being higher in dark and lower in light skin phenotypes (34-36).

Although skin, eye, and hair coloration is largely determined by genetics (33,35), multiple intrinsic pathways (i.e., endocrine, immune, inflammatory signals) and extrinsic factors (i.e., UV light intensity, environmental pollution) are also involved in modulating the pigmentation patterns within and between populations (33,35-38). Notably, the localization of Ang II and its receptors in the skin, particularly the expression of functional AT1R in melanocytes, has been suggested to play a role in this regard. Apart from the well-established cardiovascular effects, Ang II has also been indicated to play an additional role in human skin pigmentation via the regulation of the melanogenic pathway (39-41).

Liu et al., exploring the effects of angiotensin on melanogenesis, recently demonstrated an increased tyrosinase activity and melanin content in human cultured melanocytes following AT1R stimulation in response to treatment with Ang II (39). These findings provide evidence to suggest an association between Ang II, tyrosinase and AT1R activation, supporting a stimulatory melanogenic effect of Ang II, which may be involved in cutaneous pigmentation.

Apart from defining an important phenotypic trait, melanin appears to play a major role in the natural photoprotection of skin (42,43). In evolution, skin pigmentation in the human lineage has developed via a process of natural selection primarily to protect the skin from the damaging effects of solar UV radiation (UVR) (44). Since UVR can exert cytotoxic, mutagenic and immunosuppressive effects, either by direct action on DNA or indirectly by generating reactive oxygen species (ROS) and oxidative stress, the epidermis has been armed with melanin to maintain and/or restore local homeostasis against the UVR-driven insults (37,42,43,45). Melanosomes, by forming supranuclear caps, protect keratinocytes from solar UV-induced DNA damage, while eumelanin acts as a direct scavenger of ROS generated upon UV exposure, reducing oxidative cellular damage (34,42,43).

However, along with the well-known radical scavenging and antioxidant properties, an increased skin melanin content has long been recognized to be inversely related to the vitamin D status (32), which may probably account for the observed ethnic differences in vitamin D deficiency. Vitamin D is primarily obtained from 7-dehydrocholesterol (7-DHC) in the skin through solar exposure, with the UVB spectrum (290-315 nm) mostly contributing to its endogenous photosynthesis (22,46,47). In fair-skinned individuals, short periods (20-30 min) of midday sun exposure 2-3 times per week is sufficient to achieve and maintain an optimal 25-hydroxyvitamin D [25(OH)D] status. However, this exposure pattern cannot be applied to darker skin populations (skin types V-VI), as well as the elderly who require higher weekly UVR doses to meet vitamin D needs. The equivalent exposure time or frequency for these specific groups has been estimated to be 2- to 10-fold higher compared to white-skinned, young Caucasians (47-49).

In fact, melanin can act as an effective natural filter by absorbing and scattering UVR, thereby impairing the solar UVB-mediated conversion of 7-DHC to pre-vitamin D3 (32,45,47,50,51). As a result, the skin photosynthesis of 25(OH)D3 can be reduced by as much as 99% (32). This places dark-skinned individuals at higher risk for hypovitaminosis D than light-skinned ones and is particularly important in northern regions where pigmented skin (non-white ethnicity) is considered the major risk factor for vitamin D insufficiency/deficiency across all age groups (47,50). Previous studies have consistently provided evidence to support the ethnic aspects of vitamin D inadequacy, demonstrating a higher prevalence in people with naturally darker skin (52-54). Of note, skin hyperpigmentation has also been recognized as a key risk factor for hypovitaminosis D in sunny lower latitudes, such as Australia (47).

Intriguingly, various biological functions affecting human health and disease have only recently been attributed to melanin pigments, but remain largely unexplored. In this respect, less clear is the link between melanin and immunity (55). However,
accumulating evidence from several systems suggests that melanosomes are potent immunomodulators with both pro- and anti-inflammatory properties, depending on the type of melanin and host response (56). In humans, host melanin has long been implicated in the setting of ocular and gingival inflammatory disorders (57-59). Using a murine model, Kaya et al demonstrated an enhanced intraocular inflammatory response to uveitis in heavily pigmented eyes, possibly as a result of the pro-inflammatory effects of melanin (59). Similarly, in the human gingiva, a significant positive correlation between melanin distribution and presence of gingival inflammation has also been reported (57).

It should also be emphasized that melanin is considered to affect inflammatory responses directly and/or indirectly by influencing the host cytokine/chemokine production (56). Both in vitro and ex vivo data have indicated that melanin can modulate cytokine-mediated signaling cascades, increasing the release of pro-inflammatory mediators, such as interleukin (IL)-1, IL-6, interferon γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Additional evidence supporting a potential role of melanin in the course of host immune responses during infection is provided by in vitro findings demonstrating a melanin-induced activation of the nuclear factor-kB (NF-kB) in monocytes through a Toll-like receptor (TLR)-dependent process (55,60). A key question that remains to be addressed is whether or not these pathways could elicit an excessive immune response that may ultimately lead to tissue damage through a vigorous inflammatory reaction (55,61).

Although the interactions between the pigmented and immune system have not yet been fully elucidated, melanocytes, as a melanin source, have been reported to normally exist in oral and nasopharyngeal mucosa (62-64). These findings could thus pave the way for further consideration in different populations to translate heterogeneous basic research into a clinical perspective relevant to infectious disease, including SARS-CoV-2.

5. Vitamin D in respiratory antiviral defense

Several lines of evidence suggest that the vitamin D endocrine system is involved in multiple biologic processes and pathways, affecting not only musculoskeletal health, but also a variety of apparently different disease models, including infectious disease (46,65-67). Apart from its classical role in calcium and bone homeostasis, a modulatory role of vitamin D in immunity, inflammation and epithelial repair has previously been described (68,69). The active metabolite 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] has long been recognized to possess immune regulatory properties. Vitamin D receptors (VDRs) are widely present in immunocompetent cells, such as antigen-presenting cells, T- and B-cells. By binding to VDR, 1,25(OH)2D3 modulates and downregulates adaptive, but enhances innate immunity and improves redox balance, thus counterbalancing inflammation on multiple levels (70,71).

A growing number of studies have demonstrated that vitamin D can contribute to the defense against viral infections; notably, acute upper respiratory tract infections (21,72-80). Indeed, 1,25(OH)2D3 has been shown to exert antiviral effects, either directly by inhibiting viral replication, or via an anti-inflammatory and immunomodulatory mode of action (69,81). Although the underlying mechanisms are very complex, vitamin D appears to support antiviral immunity by targeting three distinct pathways: physical barrier, cellular natural immunity, and adaptive immunity (79).

Vitamin D helps in preserving the epithelial intercellular junction integrity, which improves host mucosal defense against pathogen invasion (15,68,82). At a cellular level, vitamin D metabolites have long been known to support innate antiviral responses in part by up-regulating antimicrobial peptides, such as human cathelicidin and defensins, to promote autophagy (68-70,83). The adaptive immune effects of vitamin D include the inhibition of Th1/Th17 CD4+ T-cells and cytokines, such as TNF-α and IFN-γ, along with stimulatory actions on Th2 and regulatory T-cells (Tregs) (69,70,84,85). By downregulating early pro-inflammatory signaling in favor of an anti-inflammatory Th2/Treg profile (69,70,85), 1,25(OH)2D3 can suppress the altered cytokine milieu induced by viral and bacterial stimuli, as observed in COVID-19 patients, thus reducing the risk of extensive tissue damage due to uncontrolled inflammation (Fig. 1) (15).

Of note, vitamin D has also been shown to exert beneficial effects on local ‘respiratory homeostasis’ (69). Although several mechanisms may be involved in this regard, there are available data suggesting that vitamin D/VDR signaling may exert lung-protective effects at least partially by regulating the balance between key elements of the RAS (86-88). In fact, an inverse correlation between the vitamin D/VDR and RAS cascades has already been described. As vitamin D may act as a potent negative endocrine regulator of the RAS, vitamin D deficiency has been proposed as the other face of RAS overstimulation (89,90). Considering that both systems have evolved in a similar and parallel manner, participating in the regulation of inflammatory and immunologic processes, as well as the presence of vitamin D (VDR) and RAS (AT1R) receptors in almost the same tissues, this link seems even more plausible (89).

Indeed, previous in vitro and in vivo experimental studies have demonstrated that the vitamin D/VDR pathway may trigger the ACE2/Ang-(1-7)/MasR axis, while inhibiting renin and the classical ACE/Ang II/AT1R cascade (86,91,92). As ACE2 can directly exert lung-protective effects, whereas ACE exhibits an opposing function (93,94), such evidence further supports the protective function of the vitamin D endocrine system in lung tissue (86-88). This feedback relation is also evident in other pathologies that are not discussed in this review but have been well documented, such as hypertension and chronic kidney disease (89).

6. Implications of vitamin D for COVID-19

Since vitamin D deficiency and/or insufficiency has emerged as a global pandemic linked to an increasing number of non-skeletal disorders, the importance of vitamin D/VDR signaling in overall health and well-being has attracted increasing attention in recent years (65-67,95,96). Hypovitaminosis D has also been recognized as an independent risk factor for total mortality in the general population (95,97).

Although randomized controlled trials and large-scale cohort studies investigating the links between the vitamin D status and COVID-19 incidence and severity are currently
limited, evolving epidemiological evidence supports the hypothesis that vitamin D inadequacy can negatively affect COVID-19 outcomes (14,15,20,98).

The outbreak and peak of SARS-CoV-2 in wintertime, when vitamin D levels drop to their lowest, as well as the pattern of geographical spread of COVID-19 seem to reflect higher population rates of vitamin D deficiency (15,20,98).

Of note, COVID-19 associated fatality rates appear to coincide with vitamin D deficiency rates, with northern mid-latitude countries, where vitamin D deficiency is still widely prevalent, bearing a greater burden of morbidity and mortality (15,20,98).

Moreover, a striking overlap between the high-risk groups for severe COVID-19 and vitamin D insufficiency has already
been reported. Indeed, severe COVID-19 infection and hypovitaminosis D appear to share numerous risk factors, including advanced age, male sex, obesity, darker skin pigmentation, inadequate sunlight exposure, and chronic disease comorbidity, particularly hypertension, cardiovascular disease, and diabetes (14,16,98,99).

To further support this hypothesis, several clinical and observational studies have thus far demonstrated an inverse correlation between vitamin D status and COVID-19-associated morbidity and mortality (15-17,20,100). Cross-sectional analyses in 20 European countries have reported a significant negative association between the mean vitamin D levels and the number of COVID-19 cases/1 million population (16) and between the average vitamin D levels and COVID-19-related deaths/1 million population (100). A recent review comprising 188 studies (47 original human research studies) on the relation between vitamin D and COVID-19 also provided biological plausibility supporting the assertions that vitamin D deficiency can explain every major risk factor, including the mystery of why elderly males and individuals with naturally melanin-rich skin are especially vulnerable, as well as every complication of COVID-19 (15).

From a biological perspective, there is compelling evidence to indicate that the vitamin D/VDR pathway can favorably modulate the host immunity to SARS-CoV-2, both in the early viraemic and later hyperinflammatory stages of COVID-19. In fact, vitamin D deficiency seems to compromise innate immune functions, increasing the risk of viral infections in the respiratory epithelium, including COVID-19 (14,15). Despite the sparse laboratory data regarding the impact of vitamin D on host responses to SARS-CoV-2, a recent in vitro study explored four compound libraries for antiviral activity demonstrating a direct inhibitory effect of calcitriol (the active form of vitamin D) on human nasal epithelial cells infected with SARS-CoV-2 (101).

However, it is the impact of vitamin D on unregulated cytokine production and, potentially, on the severity/risk of ARDS that is of particular importance in COVID-19 (15,17,102). In this respect, the finding that vitamin D deficiency may increase the potential for cytokine storm by deregulating the X-chromosome-linked RAS appears to be much more specific in the context of severe COVID-19, where overactivation of the RAS has been associated with a poorer prognosis (14,15).

Although conclusive scientific data may eventually be available, such correlational evidence might be of great interest in darker-skinned individuals, who are more likely to be vitamin D deficient, as it points toward an aberrant inflammatory response if exposed to SARS-CoV-2, possibly indicating a higher risk of COVID-19 adverse outcomes.

A schematic diagram of the vitamin D/VDR and melanin related signaling pathways along with their potential implications for COVID-19 is presented in Fig. 2.

7. Conclusions

In summary, the present review attempts to broaden current knowledge of host biological factors, such as vitamin D status and melanin polymers, possibly related to clinical outcomes of COVID-19. Although contradictory data exist, vitamin D may turn into an effective adjuvant to mitigate the impact of the current pandemic, especially in populations where hypovitaminosis D is prevalent. Notably, the concept of vitamin D regulation of cytokine storm through the RAS opens up new perspectives on the functions of vitamin D/VDR signaling, providing a basis for exploring the potential use of vitamin D analogs in the prevention and/or treatment of COVID-19.

Given that vitamin D is a safe, inexpensive, and widely available agent, even in countries with limited resources, vitamin D inadequacy is obviously an easily modifiable risk factor. Therefore, from the literature reviewed here, prevention and/or restoration of vitamin D deficiency/insufficiency through vitamin D supplementation during the COVID-19 period seems to be highly supported by the evidence.

For greater benefits, however, consideration of basic biological variables, especially in different population settings, is clearly warranted as the COVID-19 infection rates are once again on the rise. At this point, our study might provide early insights into a range of mostly overlooked host factors throughout the disease pathway. Besides the well-known limiting effects of melanin on the cutaneous biosynthesis of vitamin D, which could negatively affect COVID-19 outcomes, the potential interplay between the pigmented and immune system may also require special emphasis regarding the current pandemic. Further research is needed to address these observations and elucidate whether any of the implicated effects could be specific to SARS-CoV-2.

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Authors’ contributions

DC conceived the presented idea, while PS retrieved the data and wrote the manuscript under the supervision of ND. ND aided in data extraction and revised the manuscript critically. PS and AOD designed the figures. AOD, VN, MSK, DAS and AT contributed to the editing and revision of the manuscript. All authors have read and agreed to the final version of the manuscript.

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