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COVID-19 pandemic and vitamin D deficiency: a different approach with an analysis of the findings and a complimentary proposal

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Abstract

Vitamin D is an essential immune-modulator with receptors widely distributed throughout the body, and its serum levels fluctuate significantly in individuals between winter and summer months. This study examines the association between low vitamin D status and prevalence of COVID-19 cases around the world and proposes a relationship with the seasonal character of the human immune system strength rather than to the seasonal infectivity of viruses. Also, this review suggests that the observed geographical disparities in COVID-19 cases are due to differences in vitamin D levels. On the international scale, serum vitamin D levels are reportedly lowest in China, the Middle East, and South Europe; these populations also had the largest outbreaks of COVID-19 cases. In addition to the geographical differences in vitamin D status, there are known risk groups (ethnic, age-related, pregnancies). In contrast, some countries including Canada, Finland, and North Europe incorporate increased amounts of vitamin D through fortified foods, vitamin D supplements, and sunbathing. These countries show the lowest morbidity and mortality rates by COVID-19 infection and demonstrate that lower ambient temperatures do not contribute to a higher number of COVID-19 cases. COVID-19 has spread around the globe almost simultaneously in both warm and cold areas. Given this information, vitamin D measurement should become an essential component of public health monitoring as a biomarker of immunity status. Clinical trials should be conducted to confirm this hypothesis. COVID-19 tests should be performed together with vitamin D status tests to verify this proposed relationship.

Keywords: *COVID-19; geographical differences; seasonal immune system; vitamin D deficiency; vitamin D status.*

1. Introduction

The morbidity and mortality due to COVID-19, not only depends on the virus but also on the patient's responses against this infection. The immune defenses play a leading role in the survival rate of infected patients (Raoult et al., 2020). It is well known that vitamin D is an important modulator of the immune system (Aranow 2011; Arnljots et al., 2019), which would influence the susceptibility to be affected by COVID-19.

Serum vitamin D or 25-hydroxyvitamin D (25(OH)D) levels rise with the dermal exposure to sunlight and fall during the “dark months” of the year (November to March– in the northern hemisphere), fluctuating from 30 to 50% in some cases (Lips et al., 2019; Grant et al., 2017; Cinar et al., 2014). Vitamin D status depends on its intake through the diet or supplements, but most of it (50% and 90% of vitamin D in the body) depends on its dermal synthesis under the influence of ultraviolet radiation. In addition to sunlight exposure, the production of vitamin D in the skin is modulated by latitude, skin-covering clothes, the use of sunblock, and skin pigmentation. Sun exposure has altered dermal structure throughout evolution, and currently 6 skin types are identified (Fitzpatrick scale) that synthesize vitamin D at different rates (Lips, 2010), where the pale skin is the most efficient and the dark skin is the least efficient (Grant et al., 2017; Lips, 2010).

Unlike melatonin, whose synthesis uniquely increases in the pineal gland at night, the biosynthetic pathways of vitamin D are directly related to sunlight exposure (Mocayar Marón et al., 2020). The synthesis of epithelial melanin (as influenced by melatonin) in the skin, reduces vitamin D production (Álvarez-Artime et al., 2020); thus melatonin and vitamin D are inversely related. Both vitamin D and melatonin have critical immunomodulatory effects, with vitamin D stimulating the immune system during the day and melatonin maintaining its activity during darkness (Mead, 2008).

In addition to its non-enzymatical synthesis, vitamin D is enzymatically converted into its active form 1,25-(OH)2D mainly in kidneys and liver, and also somewhat in other tissues such as prostate, placenta, lungs, brain, and immune cells (Adams & Hewison, 2012; Zehnder et al., 2001). Vitamin D is a steroid hormone with 1,25-(OH)2D being the ligand for vitamin D receptors (VDR). Cells lacking the VDR are the exception and their widespread distribution underlies the potential myriad of physiological actions for vitamin D (Rosen et al., 2012). Moreover, vitamin D homeostasis is achieved only within a specific range; both excessive and insufficient levels being equally bad. This characteristic would explain why daily supplementation with physiological doses of vitamin D3 usually yields better results than bolus charge supplementation (Alshahrani & Aljohani, 2013).

An international consensus about the definition of vitamin D deficiency and sufficiency is still lacking, but the Institute of Medicine defines a 25(OH)D concentration of 50 nmol/L (20 ng/mL) as the threshold of sufficiency (Ross et al., 2011). The same definition has also been adopted by the European Food Safety Agency (Lips et al., 2019). Nevertheless, vitamin D deficiency, defined as serum 25(OH)D levels <50 nmol/L or <20 ng/mL, represents a worldwide public health problem that affects at least one billion people (Alshahrani & Aljohani, 2013). One of the primary causes of the epidemic vitamin D deficiency worldwide is the lack of sun exposure (Cinar et al., 2014); as a result, this deficiency may increase with confinement of people in their homes during any pandemic, including the current COVID-19 outbreak. Traditional risk groups for vitamin D deficiency include pregnant women, children, elderly people and dark skin people (Martín Giménez et al., 2020). Especially in the Middle-East and Asia, vitamin D deficiency in adults is highly prevalent (Van Schoor & Lips, 2011). Furthermore, our group showed that there may be a relationship between inflammatory processes induced by chronic over-stimulation of the renin-angiotensin system (RAS) and the worldwide deficiency of vitamin D. Therefore, low vitamin D levels may represent an important risk factor for the development of several diseases related to RAS over-activation, such as infectious, autoimmune, neurodegenerative, and cardiovascular diseases, as well as diabetes and cancer (Ferder et al., 2013; Giménez et al., 2020). Figure 1 shows some of the main causes of vitamin D deficiency which could contribute to the morbidity and mortality of COVID-19.

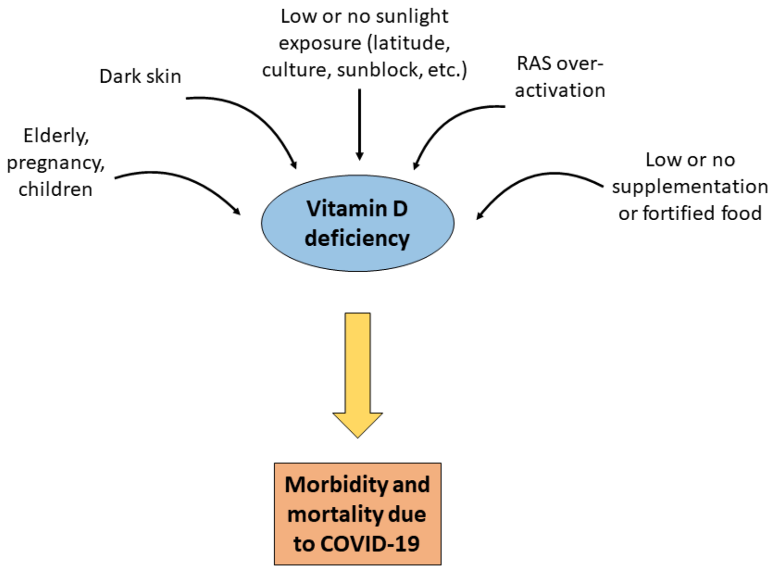

Figure 1 Risk factors for vitamin D deficiency which could predispose to COVID-19

2. Vitamin D status around the world and its role as an immunomodulatory/antiviral agent in respiratory infections

An analysis of vitamin D status in Europe and Middle-East found that vitamin D deficiency occurs in <20% of the population from Northern Europe, in 30–60% from Western, Southern and Eastern Europe and up to 80% from Middle East countries. Moreover, severe deficiency (serum 25(OH)D <30 nmol/L or 12 ng/mL) is reported in 12.5% of Europeans (Lips et al., 2019).

Skeletal consequences of vitamin D deficiency include mineralization defects and lower bone mineral density, which causes fractures. Extra-skeletal consequences include muscle weakness, falls, and acute respiratory infections, which are the subject of large ongoing clinical trials (Lips et al., 2019). However, older people with hip fracture usually die from pulmonary infection rather than from the bone fracture (Panula e al., 2011). An extensive systematic review from 2017 carried out on a sample of 10,933 participants from 0-95 years, reported that vitamin D supplementation reduced the risk of acute respiratory tract infection in all participants (Martineau et al., 2019), which suggests that vitamin D has a key role in mediating the immune response to infection (Bikle, 2009). Furthermore, many studies demonstrated that the highest influenza rates are closely related with lowered serum 25(OH)D concentrations. Thus, although the risk of influenza may be affected by environmental temperature and especially by absolute humidity (which is able to considerably modulate the airborne transmission and survival of different viruses such as influenza) (Shaman et al., 2010), 25(OH)D concentrations may be a determining factor in the infective process (Grant et al., 2017). Moreover, cell culture experiments provide evidence that vitamin D has direct anti-viral effects, particularly against enveloped viruses (Beard et al., 2011). In this regard, Cannell and colleagues (2006) proposed that influenza epidemics are usually seasonal, mostly a result of seasonal variations in solar ultraviolet B (UVB) doses and serum 25(OH)D concentrations. Likewise, it was suggested that increasing the mean serum 25(OH)D level to 105 nmol/L could reduce global mortality rates by 37,000 deaths annually (16,1%) (Grant et al., 2010). Another report estimated that doubling serum 25(OH)D concentrations at the global population level could lower mortality rates by 10–20%, adding about 2 years to overall adult life expectancy (Grant, 2011).

To reiterate, scientific evidence shows that advanced age is associated with significantly reduced dermal synthesis of vitamin D; aging also depletes the endogenous production of many other hormones, including the immune stimulator melatonin, especially in the frail elderly (Scholtens et al., 2016). Vitamin D and melatonin are responsible for mitochondrial homeostasis and lack of both or one leads to increased oxidative stress, inflammation, and mitochondrial dysfunction, which cause the worsening of different pathologies, including respiratory diseases (Mocayar Marón et al., 2020; Martín Giménez et al., 2020b) such as COVID-19.

3. Seasonal character of the immune system and its influence on global mortality rate from COVID-19

World Bank data related to mortality rates in Europe from 1960 to 2018 show a significant rise after 2008, which is in accordance with existing data about the vitamin D levels which were lower in 2000s in comparison with previous decades. Recent mortality rates have risen by 8-11% in most West and South European countries, but not in North European countries (https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?end=2018&locations=NO-SE-DK-FI-IE&start=2008/). The available data show that the lowest mortality rates were observed during the summer months in both 15-64 and 65+ age groups. Moreover, almost a 2-fold rise in mortality rates in 65+ compared to the 15-64 group was reported (Lips et al., 2019; Van Schoor & Lips, 2011). These results may be explained by the higher seasonality fluctuations in the immune system, and not the seasonal character of viruses (viruses are constantly fluctuating throughout the year, especially in children) (Barnard & Colón-Emeric, 2010; Gavigan & McCullers, 2019). Coronaviruses have been a well-known cause of colds for decades. Children usually have 6-10 colds per year. Adults generally have 2-4 colds per year on average. Children are also a risk group for vitamin D deficiency, which may explain the increased number of colds per year in this group. Although this does not produce deaths in children, probably due to the adequate internal synthesis of protective molecules such as melatonin and the protection conferred by thymus (which remains functional to puberty) against infections. Children may be a constant reservoir of viruses in society (Zisi et al., 2019; Rondanelli et al., 2018).

Xie and Zhu (2020) found no evidence documenting that case counts of COVID-19 decline when the weather becomes warmer if the temperature is above 3 °C. Cases observed in Ecuador confirmed that the COVID-19 outbreak can also happen at 30° C. These data strongly confirm the non-seasonal character of coronavirus. Also, Iran, with a hot/dry climate and mild temperatures in March, was affected by a large number of COVID-19 cases. Casually, Iran, as well as Saudi Arabia and Egypt, have some of the lowest serum levels of vitamin D in the Middle East (Chakhtoura et al., 2018). Falling European mortality rates during summer months could mean that immune response is more robust in this season both in adolescent and adult population, due to increased serum vitamin D levels related to a high sun exposure, which starts to drop significantly when day length decreases (Spiro & Buttriss, 2014). The same pronounced seasonality in mortality rates has been observed in the USA, which could be associated with factors that show seasonal variations such as solar UVB doses and serum 25-hydroxyvitamin D [25(OH)D] concentrations, gene expression, environmental temperature and humidity, among others. However, the factors with the most reliable support are seasonal variations in solar UVB doses and 25(OH)D concentrations (Grant et al., 2017), although there are other wavelengths of the visible and near-visible electromagnetic spectrum that also directly impact on cellular physiology (Zimmerman & Reiter, 2019). Thus, seasonal variations in temperature seem to play a minor role in the susceptibility to COVID-19 (Grant et al., 2017). Supporting this, the Middle East respiratory syndrome (MERS) epidemic appeared in September 2012, which cannot be explained by a significant drop in environmental temperatures. Some studies show that Middle East vitamin D deficiency occurs in 80% of the population (Chakhtoura et al., 2018). This low vitamin D status in Saudi Arabia may be the main reason why the population became vulnerable to acute respiratory infections in September rather than in mid-December, when vitamin D levels start to drop more meaningfully (3 months after they peak) (Chakhtoura et al., 2018; Bassil et al., 2013). Another report claimed that cardiovascular disease (which contributes to death by COVID-19) rates are usually higher in winter than in summer, regardless of whether the country is extremely cold, as in Kazakhstan (Rosano et al., 2019), or hot as in Kuwait (Van Schoor & Lips, 2011). Therefore, seasonal variations in solar UVB doses and/or serum 25(OH)D concentrations seem the most likely reasons for causes of death by COVID-19 (Grant et al., 2017). Figure 2 shows the seasonal character of immune system and the level of susceptibility to COVID-19, as a consequence of seasonality of vitamin D status.

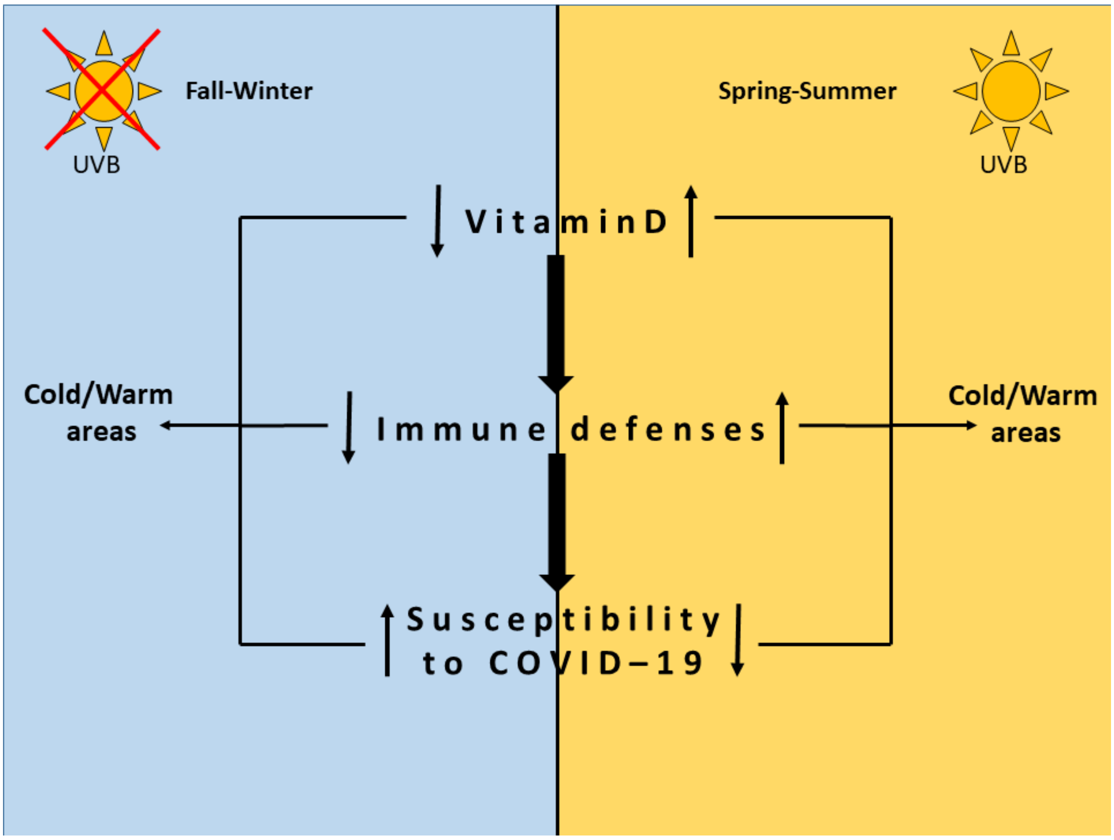

Figure 2 Influence of seasonal character of the immune system and vitamin D status on the susceptibility to COVID-19

4. Vitamin D status as a predictor of the susceptibility to COVID-19 infection in the world population

The potential antiviral effect of vitamin D has recently been suggested by researchers from Iran (Teymoori-Rad et al., 2019). Another research group showed that people with a mean monthly serum 25(OH)D concentration of >38 ng/mL (>95 nmol/L) during the fall-winter period had less than half the incidence of acute viral respiratory infections as reported in those with lower serum vitamin D concentrations (Sabetta et al., 2010). An ecological study found that communities exposed to higher solar UVB doses -both in summer and in winter-, had a significantly lower mortality rate during the pandemic influenza of 1918–1919 in the USA (Grant & Giovannucci, 2009). The proposed antiviral and immunomodulatory mechanisms of vitamin D included the induction of cathelicidin (or LL-37) synthesis, an important epithelial antimicrobial peptide. The well-known antimicrobial and anti-endotoxin properties of cathelicidin would protect against respiratory infections and reduce the severity of the inflammatory response induced by cytokines (Martineau et al., 2019; Beard et al., 2011). A study in South Korea found that a serum 25(OH)D concentration >20 ng/mL was associated with an adjusted odds ratio for mortality of 0.94 (95% CI, 0.90–0.99) for those individuals who developed community-acquired pneumonia (Kim et al., 2015).

As previously mentioned, a link between vitamin D status and skin coverage/type is also known. Of interest, vitamin D deficiency is prevalent in the Middle East, where the use of clothes that cover skin and avoid the sunlight may explain this deficiency. Iran is the most profoundly affected by COVID-19 among Middle East countries. A poor to moderate vitamin D status is also common in Africa, probably caused by the dark skin types (Martín Giménez et al., 2020a). Vitamin D status is much better in North America, where vitamin D deficiency is uncommon, but vitamin D insufficiency is still usual. The generally higher levels of vitamin D in North America are because in Canada, milk is habitually supplemented with vitamin D, and the use of vitamin D supplements is relatively standard. This situation may explain the low mortality rate due to COVID-19 in this country. Moreover, a better vitamin D status in the Nordic countries than in the Mediterranean region may also be due to the lighter skin of their inhabitants, greater sunlight exposure and higher consumption of cod liver oil than in Southern Europe, where people stay out of the sunshine and naturally have a darker skin color (Lips, 2010).

Furthermore, the higher mortality by influenza observed in Italy compared to other European countries, may be attributable to the high percentage of elderly people in this country (Rosano et al., 2019). The combination of age and low vitamin D status in Italy may explain higher mortality rates from influenza as well as COVID-19. Also, some studies from the USA in 2012 showed that influenza vaccinations reduced the risk of influenza to some extent, but the effect seemed to be higher for children than for elderly people. The administration of a three-strain vaccine in the 2010-2011 influenza season was 69% effective for children from 6 months to 8 years, but only 38% effective for adults older than 65 years (Treanor et al., 2012), which may be related to differences in vitamin D status between both age groups.

Reinforcing the evidence presented in this review, several registry-based observational clinical It is also noteworthy that the vitamin D status in India is weak to moderate, and 40% of the Indian population does not have access to clean water and soap; despite this, India has not experienced any major epidemics thus far. However, China, where vitamin D status is lower than India, had a high incidence of COVID-19 (Lips et al., 2019; Van Schoor & Lips, 2011). This may be because, as a general rule, Chinese people admire white skin in comparison with black skin, and tend to avoid sunlight exposure in order to keep their skin clear (Dobson, 2007). Thus, this factor may be a main reason why viral pandemics are initiated in China more frequently than in other countries.

Studies from different countries have been already examined an association between low plasma vitamin D level and increased risk of COVID-19 infection (Merzon et al., 2020; D'Avolio et al., 2020; Meltzer et al., 2020).

5. Conclusion and prospects

There is a well-established seasonality in human mortality rates by COVID-19, which indicates the seasonal character of the immune system. This seasonal character depends mainly on two immunomodulatory hormones: vitamin D and melatonin. Children up to 15 years of age are well protected from the deficiency of vitamin D by abundant amounts of melatonin and that do not exhibit seasonal fluctuations in their immune system.

Of special interest, China may continue to be the cradle of new viruses because of inadequate vitamin D status. The best example of good practices is Canada, where, despite its latitude, there is low vitamin D deficiency and COVID-19 deaths are among the lowest in the Northern hemisphere.

It is essential to highlight the importance of vitamin D and the maintenance of its homeostasis in multiple organs (especially lung, brain, immune cells) in order to prevent different severe chronic diseases as well as acute respiratory infections such as COVID-19. The prevention of vitamin D deficiency requires moderate sunlight exposure (sunbathing in cold temperatures was used in tuberculosis treatments before the antibiotics era), consumption of fish, fortification of foods, and the use of vitamin D supplements, among others. Also, it may be advisable to introduce active monitoring of vitamin D status for public health reasons. In this regard, the normalizing of vitamin D status could be useful for treating or preventing this and similar affection.

It is important to test the hypothesis that the use of high doses of vitamin D supplementation added or not to usual doses of melatonin, may help to improve the response against COVID-19, thereby reducing pulmonary and cardiovascular complications, and finally, decreasing the death rate of high-risk populations.

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