Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short Communication

Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate

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ABSTRACT

The world is desperately seeking for a sustainable solution to combat the coronavirus strain SARS-CoV-2 (COVID-19). Recent research indicated that optimizing Vitamin D blood levels could offer a solution approach that promises a heavily reduced fatality rate as well as solving the public health problem of counteracting the general vitamin D deficiency. This paper dived into the immunoregulatory effects of supplementing Vitamin D_3 by elaborating a causal loop diagram. Together with D_3, vitamin K_2 and magnesium should be supplemented to prevent long-term health risks. Follow up clinical randomized trials are required to verify the current circumstantial evidence.

Introduction

The COVID-19 pandemic is a current pandemic of high international interest, caused by the coronavirus strain SARS-CoV-2. Up to date, there is no treatment to decrease the virus-caused infection and mortality rates (Cortegiani et al., 2020). More and more voices are being raised supporting the supplementation of Vitamin D_3 to counter the pandemic outbreak with the correlated mortality rates as well as economic and social consequences (Grant et al., 2020). In a recently published review article, Sharma et al. (2020) have critically discussed the association of vitamin D with viral infections. A recent clinical study from Iran (n = 611) stated that there were no COVID-19 deaths in a hospital if serum 25(OH)D concentrations were higher than 41 ng/mL and patients were younger than 80 (Maghbooli et al., 2020). Russian hospitals observed that the likelihood to have severe COVID-19 increases by the factor of 5 if vitamin D is deficient (Karonova et al., 2020). Similar observations have been made by Panagiotou et al. (2020). Tan et al. (2020) observed a significant reduction in oxygen support for older clients when providing them with a relatively low daily dose of 1000 IU D_3 OD, 150 mg magnesium OD, and 500 μg B12 OD upon admission. On the other hand, one retrospective cohort study that investigated the correlation between the mean D3 serum levels of different European countries and the COVID-19 mortality rate was not considered significant (Ali, 2020). An explanation for this could be that testing conditions differ in each European country, making it difficult to reach a conclusion in such a retrospective study. Also, the mean D_3 serum levels do not necessarily apply to people who are especially vulnerable to that virus (e.g. aged and bedridden people). This assumption is supported by De Smet et al. (2020) who documented a significantly lower median D_3 value in patients with COVID-19 compared to control subjects.

The obviously correlating vitamin D deficiency is linked to increasing the risk of many common and serious diseases (Holick, 2004). In a study conducted by Forrest and Stuhldreher (2011), vitamin D deficiency was defined as a serum 25(OH)D concentrations $\leq$20 ng/mL. 41.6% of the test subjects have been considered vitamin D deficient. Of the tested people of color (PoC) and Hispanics, the deficiency rate was even 69.2% and 82.1%, respectively. Similar observations with respect to patients' ethnicity have been made by Holick (2002) and Darling et al. (2020). The latter also states that serum 25(OH)D concentrations were lower in obese people that were tested COVID-positive, which is most likely due to increased relative body volume. Haq et al. (2016) even report that 82.5% of studied patients in the sun-intensive Middle East were vitamin D deficient. These observations with respect to common vitamin D deficiency, together with evidence of several experimental studies (Bendix-Struve et al., 2010; Casteels et al., 1998; Holick, 2005; Seibert et al., 2013), indicates that vitamin D is essential in the modulation of immune function (Aranow, 2011; Sassi et al., 2018).

The threshold of Vitamin D deficiency is a continuous subject of discussion. Whereas the European Food Safety Authority recommends a minimum serum level of 25(OH)D of 25 nmol/L (i.e. 10 ng/mL) (EFSA, 2016), many scholars consider this value way too conservative. A study that was conducted in Kenya on healthy black

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males showed that 25(OH)D levels <30 ng/mL were associated with a significant rise in physiological markers such as parathyroid hormone (PTH) (Kagotho et al., 2018). Thus, desirable 25(OH)D levels are rather to be found between 30–48 ng/mL (Bischoff-Ferrari, 2008; Raftery and O'Sullivan, 2015; Vieth, 2011), i.e. 3–5 times higher than recommended by the European authorities. Looking into optimal 25(OH)D serum levels from an epidemiological and evolutionary perspective could be another approach to getting a rough indication on these levels (Carlberg, 2019; Luxwolda et al., 2012). It has been shown that traditional African hunter-gatherers had an average serum level of 48 ng/mL.

This publication set out to show the metabolic pathways behind the immunomodulating effect of vitamin D by following a systems thinking approach. The output will also give advice on which other dietary supplements one should consider.

Methodology

One of the basic principles that is used to combine valuable scientific findings and knowledge from often interdisciplinary domains is called systems analysis. Causal loop diagrams (CLDs) functioned as a tool to illustrate the principle of causality of 25(OH)D serum levels on the human metabolism and form the basis for systems analysis (Mabin et al., 2006). Such causal loop diagrams are powerful instruments for problem identification and problem resolving purposes by breaking down a comprehensive system into fragments in order to enhance its comprehensibility (Haraldsson, 2004).

Visualizing concepts makes it much easier to understand complex correlations and casualties (i.e. cause and effect mechanisms). The problem (in this case immune systems that have difficulties coping with COVID-19) stands in the center of the systems analysis. Data on the impact of vitamin D_3 on the immune system have been collected and elaborated in the results and discussion section. Based on these findings, the CLDs have been created and digitized using the Vensim software (Ventana Systems, 2015).

Results and Discussion

Figure 1 illustrates a causal loop diagram coping with the effects of vitamin D_3 and K_2 supplementation. The diagram will be elaborated and discussed throughout this section.

In a simplified scheme, the majority of the previtamin D_3 is both acquired in the human skin from the conversion of 7-dehydrocholesterol through cutaneous solar ultraviolet radiation (Kheiri

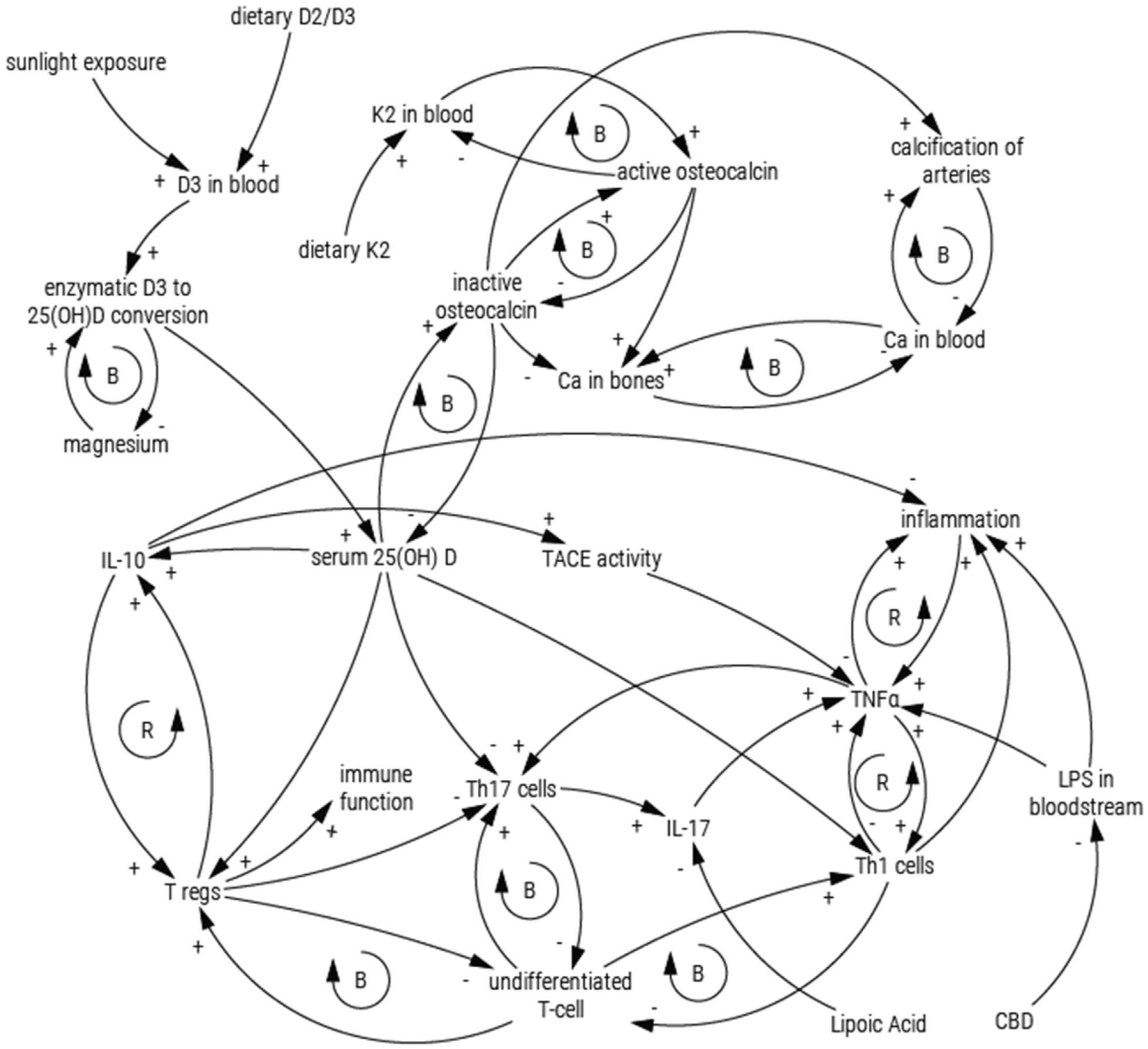

Figure 1. Causal loop diagram of the impact of vitamin D3 on the immune system.

Table 1
Tabular indicator for raising the 25(OH)D blood serum levels from 20 ng/mL to 40 ng/mL and maintaining them after consultation with the physician (von Helden, 2011).

Body weight	10 days fill up	Daily D3 supplementation (IU)	Daily K2 (MK7) supplementation (μg)
50	14.000	2.200	100
60	16.800	2.600	120
70	19.600	3.000	140
80	22.400	3.500	160
90	25.200	3.950	180
100	28.000	4.380	200
110	30.800	4.820	220

et al., 2018), and to a lesser extent through dietary supplementation (D_2 and D_3). The metabolic pathway continues in the liver where D_2 and D_3 are hydroxylated to 25(OH)D. 25(OH)D is eventually transformed into 1,25$(OH)_2$Vitamin D_3 (the physiologically active form of vitamin D) in the kidneys (Keane et al., 2018). The high degree of vitamin D deficiency may not be due solely to the modern office-lifestyle (i.e. home - car - office - car - home; repeat) but also depend on factors such as higher latitude, degree of skin pigmentation, seasons (i.e. winter) and dietary intake (i.e. fatty fish, liver, fermented foods, etc.) (Mithal et al., 2009).

Oral supplementation of D_3 is the easiest means to prevent deficiencies. A frequent argument against supplementation of vitamin D_3 is that an increased intake could lead to a vitamin D toxicity, also called hypervitaminosis D (Orme et al., 2016). This again can cause hypercalcemia, which is the buildup of calcium in the blood leading to vascular calcification, osteoporosis, and kidney stones. However, it has been reported that the reason for hypercalcemia rather lays in a vitamin K_2 deficiency (Flore et al., 2013; Vermeer and Theuwissen, 2011), as K_2 activates the bone gamma-carboxyglutamic acid-containing protein (osteocalcin) through carboxylation. Activated osteocalcin deposits calcium in the bones, whereas non-activated osteocalcin inhibits calcium absorption by the bones. As the osteocalcin synthesis rate is increased by higher 25(OH)D serum levels, K_2 is required as a natural antagonist (Yasui et al., 2006; Dofferhoff et al., 2020).

It has also been observed that D_3 supplementation led to an increase in anti-inflammatory and immunoregulating interleukin 10 (IL-10) cytokines and reduced frequency in Th17 cells (Allen et al., 2012), which in turn leads to a decrease in IL-17 and the proinflammatory cytokine TNFα production, decreasing inflammatory effects in the host (Ferreira et al., 2020; Latella and Viscido, 2020). Also, Zheng et al. (2014) reported that TNFα promotes pathogenic Th17 cell differentiation. On the other hand, IL-10 reduces the activity of the TNF-α-converting enzyme (TACE) (Brennan et al., 2008). Brennan et al. (2008) also observed that lipopolysaccharides (LPS) in the bloodstream enhanced TNFα values.

Whereas Th1 and Th17 cells are proinflammatory, regulatory T-cells (Tregs) have anti-inflammatory effects. Prietl et al. (2013, 2010) proclaim that vitamin D_3 supplementation showed an increase in regulatory Tregs and a more tolerogenic immunological status in general. As illustrated in Figure 1, a chronic D_3 deficit would shift the T-cell ratio towards the inflammatory pathway. Given the fact that an abundance of Th17 cells are highly associated with autoimmune diseases (Waite and Skokos, 2011; Yasuda et al., 2019), it is therefore unsurprising that many fatal cases showed comorbidities.

There are many follow-up studies required to substantiate and consolidate the hypothesis that there is a strong correlation between low 25(OH)D serum concentrations and mortality rates. But what we know is that people with “sufficient” vitamin D blood serum levels tend to have considerably less severe symptoms caused by COVID-19 (Pugach & Pugach, 2020).

Dietary considerations

Given that vitamin D_3 is an immunoregulating hormone and can be considered safe when supplementing it together with K_2, Table 1 provides a rough guideline on how to raise vitamin D levels to desired values. Supplementation of magnesium (200–250 mg/day) should also be considered, as all enzymes that metabolize vitamin D seem to require magnesium (Uwitonze and Razzaque, 2018).

Other dietary supplementations to consider are: (1) lipoic acid has been shown to inhibit pro-inflammatory IL-6 and IL-17 production (Salinthone et al., 2010); (2) omega-3 fatty acids that are anti-inflammatory and reduce kinase excretion. Consume as a supplement or in form of cod liver oil or fatty fish (such as salmon) once or twice per week (Vasquez, 2016); (3) Cannabidiol (CBD) that promotes anti-inflammatory IL-10 secretion (Joffre et al., 2020) while preventing LPS-induced microglial inflammation (dos-Santos-Pereira et al., 2020); and (4) Green Tea, since epigallocatechin-3-gallate is the most biologically active catechin in green tea. It reduces Th17 cells and increases regulatory T-cells (Byun et al., 2014).

Conclusions

Recent COVID-19-related data evaluation showed indications that a high 25(OH)D blood serum level might have an impact on the mortality rate of coronavirus patients. Even though ethical issues might arise (Muthuswamy, 2013), the paper’s hypothesis requires clinical randomized trials to verify the circumstantial evidence. This publication illustrated the metabolic mechanisms behind that observed phenomenon. It is highly suggested to also consider K_2 and magnesium intake to avoid unintended long-term side-effects such as arteriosclerosis and osteoporosis.

Conflict of interests

The author declares that they have no competing interests in this section.

Ethics approval and consent to participate

Not applicable.

Consent of publication

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Author's contributions

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