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COVID-19 & vitamin D

a critical review of available scientific publications investigating the link between the coronavirus disease (COVID-19) and vitamin D

REVIEW PAPER

abstract.

Many of the associations made between COVID-19 and vitamin D are based on studies focusing on general upper respiratory tract infections (URTI) or bone health. When it comes to COVID-19-specific research, most existing studies are observational and are not always well-defined. Only a few rare studies are interventional and thus several questions remain unanswered or part of a heated debate: are low vitamin D levels a cause or consequence of disease, what is the exact mechanism of vitamin D in this scenario, what should be the dosage of vitamin D supplementation, and is vitamin D3 preferable or D2? Well-designed intervention studies are needed and until they deliver sufficient results it is impossible to confidently state that vitamin D supplementation aids in response to COVID-19.

However, the relationship between low vitamin D levels and positive COVID-19 tests and disease severity has already been shown in a significant number of studies. Circumstantial evidence is strong, vitamin D is a safe and cost-effective option, and it has many other health benefits that are reason enough for people to be taking it.

Effectively, there is nothing to lose from supplementation or its promotion and potentially much to gain, especially for high-risk groups.

vitamin D.

Vitamin D is a fat-soluble vitamin produced from a precursor due to the action of UVB radiation. It is subsequently converted to 25(OH)D in the liver and further to the active form (calcitriol 1, 25(OH)2D) in the kidneys or other organs. It is most known for being involved in bone metabolism, promoting calcium absorption from the intestine, but it also has an important role in normal immune function.

Vitamin D levels normally reach the lowest point during or at the end of winter and scientists often call vitamin D a "seasonal stimulus" associated with increased incidence of respiratory infections (Hope-Simpson, 1981; Berry, 2011).

Mechanisms of action

Martineau describes the functioning of vitamin D in a general immunity/URTI context as follows: "25-hydroxyvitamin D supports induction of antimicrobial peptides in response to both viral and bacterial stimuli, suggesting a potential mechanism by which vitamin D inducible protection against respiratory pathogens might be mediated. Vitamin D metabolites have also been reported to induce other innate antimicrobial effector mechanisms, including induction of autophagy and synthesis of reactive nitrogen intermediates and reactive oxygen intermediates." (Martineau, 2017)

D'Avolio et al. (2020) summarize the mechanisms through which vitamin D or 25(OH)D can reduce the risk of infections: "Induction or transcription of cathelicidins and defensins that can reduce viral replication rates and concentrations of pro-inflammatory cytokines responsible for producing inflammation and injuring the lining of lungs, leading to pneumonia, as well as the capability of vitamin D to increase the concentrations of anti-inflammatory cytokines." The latter is termed a cytokine storm (overreaction of the immune system) and has been associated with COVID-19-related acute respiratory symptoms, especially worse cases.

According to Grant (2020) "vitamin D stimulates innate cellular immunity, through the induction of antimicrobial peptides, such as cathelicidins, IL-37, and defensins. It also inhibits the cytokine storm, reducing the production of pro-inflammatory cytokines such as IFNγ and TNFα. Finally, it modulates the adaptive immune response, suppressing the Th1 response, and promoting cytokines production by Th2 cells."

studies.

The linear relationship between vitamin D status and respiratory infections had already been investigated before the COVID-19 pandemic. Association between low vitamin D serum concentrations and increased risk of acute respiratory tract infections was found in observational studies. Berry et al. (2011) report that "each 10 nmol/l increase in 25(OH)D was associated with a 7% lower risk of infection after adjustment for adiposity, lifestyle and socio-economic factors." Scientists also showed the association between impaired vitamin D metabolism and respiratory diseases (COPD, asthma) (Jolliffe, 2013). However, meta-analysis of intervention randomized controlled trial (RCT) results showed only borderline statistically significant protective effect of daily or weekly vitamin D supplementation against upper respiratory tract infections (Martineau, 2016).

More recently, a striking overlap between vitamin D deficiency (low vitamin D levels) and risk factors for COVID-19 such as obesity, older age, and darker skin (Black or Asian ethnic origin) has led researchers to hypothesize that vitamin D supplementation could hold promise as a preventive or therapeutic agent for COVID-19 (Martineau, 2020).

"Several pieces of evidence support the role of vitamin D in reducing the risk of COVID-19." (D'Avolio, 2020)

D'Avolio notes that "several pieces of evidence support the role of vitamin D in reducing the risk of COVID-19, including, as indicated by other authors, that the outbreak occurred in winter, a time when 25(OH)D concentrations are low; that the number of cases in the Southern Hemisphere near the end of summer is low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case fatality rates increase with age (>70 years) and with chronic disease comorbidity, both of which are associated with a lower 25(OH)D concentration." (D'Avolio as in Grant 2020).

Such indications led to a substantial amount of observational and few interventional studies examining the relationship between vitamin D and COVID-19.

Observational study results

- Statistically significant lower 25(OH)D levels were observed in patients positive for SARS-CoV-2, compared to negative patients (D'Avolio, 2020; Baktash, 2020).
- Vitamin D deficiency was shown to be frequent among COVID-19 patients (Pizzini, 2020).
- Low vitamin D was associated with a greater risk of testing positive (Meltzer, 2020), intensive care unit (ICU) admission (Panagiotou, 2020), disease severity, and mortality (Brenner, 2020; Maghbooli, 2020-preproof; Carpagnano, 2020, Radujkovic, 2020). Notably, the cut-off levels of low vitamin D vary between studies.
- Association between lower SARS-CoV-2 positivity rates and higher circulating 25(OH)D levels was shown (Kaufmann, 2020).

Interventional study results

- Two COVID-19-positive patients were placed on a standard dose of cholecalciferol (1000 IU daily). Vitamin D levels improved minimally compared to 2 patients on a high dose of ergocalciferol (50.000 IU) daily for 5 days (Ohaegbulam, 2020).
- Administration of a high dose of calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D endocrine system, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19 (Castillo, 2020). The study included 76 patients. 50% of untreated patients required ICU vs. 2% in vitamin D treated patients. Notably, calcifediol is a drug, not approved for supplement usage in the EU.

Whether low vitamin D levels are a cause or consequence of COVID-19 has remained a point of heated debate. For causality to be shown, well-powered intervention RCTs are needed (Martineau, 2020). RCTs are ongoing but may take some time to publish. At this time it is impossible to clearly state that supplementation helps – but the association exists.

conclusions.

Research status

It is too early to get many significant results from RCTs in patients with COVID-19, however, the relationship between low vitamin D levels and positive COVID-19 tests and disease severity was already shown in a significant number of studies – it would be imprudent to dismiss those especially because vitamin D provides a cheap and safe option.

Mitchell (2020) comments: "Circumstantial evidence is very strong, we don't have randomized controlled trial evidence, but how long do you want to wait in the context of such a crisis? We know vitamin D is important for musculoskeletal function, so people should be taking it anyway."

Mitchell also quotes Martineau: "At best vitamin D deficiency will only be one of many factors involved in determining the outcome of COVID-19, but it's a problem that could be corrected safely and cheaply; there is no downside to speak of, and good reason to think there might be a benefit".

Martineau goes on to address the question of vitamin D supplementation dose: "Pending results of such trials, it would seem uncontroversial to enthusiastically promote efforts to achieve reference nutrient intakes of vitamin D, which range from 400 IU/day in the UK to 600–800 IU/day in the USA. These are predicated on the benefits of vitamin D for bone and muscle health, but there is a chance that their implementation might also reduce the impact of COVID-19 in populations where vitamin D deficiency is prevalent; there is nothing to lose from their implementation, and potentially much to gain." (Martineau, 2020)

Even if vitamin D supplementation would not directly treat or prevent COVID-19 infection and symptoms, it would still have a great impact on general health (and general cold and flu toll) of the population in the autumn-winter-spring period.

Supplementation dose

When recommending supplementation, the question we first come across is: What are the recommended serum vitamin D levels? Different authorities define them differently and mostly not with immunity outcomes in mind.

According to the Institute of Medicine (IOM), 20 ng/mL is the cut-off which is likely to meet the needs of about 97,5% of the general population (Radujkovic, 2020). The European Calcified Tissue Society Working Group has defined severe vitamin D deficiency as a serum 25(OH)D level lower than 30 nmol/L.

According to Holick (2011), 30 ng/ml (75 nmol/L) of vitamin D should be the goal serum concentration.

To achieve higher serum levels, previously mentioned reference intakes from 400 IU/day to 800 IU/day are predicated on the benefits of vitamin D for bone and muscle health.

Grant (2020), on the other hand, states recommended doses specifically for people at risk of influenza and/or COVID-19: "To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10.000 IU/day of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/day. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L)."

Whatever the communicated daily dosages may be, they must be determined with existing local legislation and target group in mind, until researchers and authorities reach a new adapted consensus.

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