Benefits of standard dose and pulse dose vitamin D in the high-risk and confirmed hypovitaminosis D population with COVID-19: an Evidence-Based Case Report (EBCR)

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Summary

Background. The Ministry of Health guidelines in Indonesia establish a protocol for administering vitamin D to people with COVID-19 as being 1,000 to 5,000 IU per day, both for adults and older adults.

Objectives. This systematic review aims to investigate how much the optimal dose for patients with COVID-19 with high-risk vitamin D deficiency is either geriatric population or have an underlying disease.

Material and methods. A 32-year-old female patient came with positive RT-PCR nasopharyngeal swab with clinical anosmia with hypovitaminosis D, and a 60-year-old patient with shortness of breath and cough complaints, positive RT-PCR nasopharyngeal swab. Both patients were given 1,000 IU/day vitamin D.

Results. A literature search was carried out from 2019 to 2021 on several search engines such as Pubmed, Clinical Trial.gov and Google Scholar. Four studies pooled and entered review synthesis.

Conclusions. Supplementation with pulse dose vitamin D provides a clinically significant improvement, decreasing inflammatory cytokine markers in the non-geriatric population with hypovitaminosis. In the geriatric population, standard vitamin D has been shown to reduce the risk of frailty and worsening clinical features in COVID-19. As clinicians, it is important to enhance clinical awareness when recognising special populations with COVID-19 who require vitamin D supplementation above the guideline dose.

Key words: COVID-19, aged, Vitamin D.


Background

Dysregulation of the immune system occurs during coronavirus disease-19 (COVID-19) infections; vitamin D has a role as an immunomodulator. A cytokine storm is one of the complications and natural processes of COVID-19 due to immune dysregulation. Vitamin D reduces immune dysregulation caused by the cascade of pro-inflammatory cytokine release and increases anti-inflammatory cytokine titres [1, 2]. The guidelines released by the Ministry of Health in Indonesia currently establish a protocol for administering vitamin D to patients with COVID-19 as being 1,000 to 5,000 IU per day in adult and elderly populations [3].

The older adult population is special; recent studies have shown that vitamin D plays a role in the geriatric population’s nervous, cardiovascular and hormonal systems. Another effect of vitamin D is to prevent frailty and fractures; according to the consensus of the American Geriatrics Society, a recommended dose of 1,000 IU of vitamin D reduces the risk of fractures and falls. Some studies state that the elderly are at risk of vitamin D deficiency, along with decreased vitamin D intake, increased adipocyte percentage, reduced vitamin D synthesis and lack of outdoor activity [4, 5]. However, the adult population is also at risk of hypovitaminosis, the majority with comorbidities. This pandemic is becoming complex in the era of this pandemic in both older adults and adults with vitamin D deficiency [6, 7].

Vitamin D has become a national and international recommendation for people with COVID-19, and the question was raised about how much the optimal dose for patients with COVID-19 with high-risk vitamin D deficiency in geriatric older adults population or have an underlying disease.

Clinical questions

A 32-year-old female patient presented with a positive RT-PCR (Reverse Transcription Polymerase Chain Reaction) and complaints of runny nose and anosmia two days prior. There was no complaints of fever, cough, and shortness of breath. She had a previous history of hepatitis B and hyperthyroidism and did not consume any medication regularly at the time. Laboratory investigations revealed vitamin D 25-OH at a level of 24.2
ng/mL. During self-isolation, the patient was given 1,000 mg of vitamin C three times a day, 500 mg of azithromycin once daily and 1,000 IU of vitamin D twice daily according to the COVID-19 guideline treatment protocol in Indonesia. On the 7th day, a re-swab showed a positive result, which was asymptomatic. On the 14th day, the swab was negative, as well as on the 16th day.

A 60-year-old patient with shortness of breath and cough complaints and was positive swab for SARS-CoV-2 PCR. The patient was previously healthy and had no relevant medical history. She suddenly experienced complete anosmia and symptoms of pneumonia. Oral vitamin C, vitamin D, favipiravir, dexamethasone and low molecular weight heparin was given during treatment on the 10th day of hospitalisation, and the swab was positive. Serial chest imaging was performed and showed improvement. The patient was later discharged.

Material and methods

A literature search was carried out from 2019 to 2021 on several search engines such as Pubmed, Clinical Trial.gov and Google Scholar using the terminology in Table 1. Searches from the three sites were carried out by title, abstract using inclusion, exclusion, double screening and full text availability. After screening by reading the full text, four articles are included in the study. All references were reviewed using critical appraisal checklist guide from the Center of Evidence-Based Medicine. Inclusion criteria are: 1) clinical trial and observational study; 2) carried out from 2019 to 2021 and using English. The exclusion criteria were letters, viewpoints, consensus, and review studies that provided advice on the topics of COVID-19 and optimal dose for patient COVID-19 with high-risk vitamin D deficiency.
Results

Four articles were found that were eligible. After reviewing the full text, two clinical trial studies and two quasi-experimental designs were obtained. The two clinical trials conducted an intervention in the form of pulse doses of vitamin D in hypovitaminosis D patients with doses varying from 60,000 IU to 100,000 IU for seven to ten days, while in the study by Annweiler et al., the geriatric population was given regular boluses of vitamin D and were divided into three groups 1) first group – bolus 50,000 IU; 2) second group – 80,000 IU every two months after being diagnosed with COVID-19; 3) third group as a control. This study was continued a year later and became an extension study [8–11].

Discussion

It was found that COVID-19 patients had lower 25(OH)D levels compared to healthy people (11.1 ng/ml vs 24.6 ng/ml; \( p = 0.004 \)) [12]. On the other hand, hypovitaminosis D increased the risk of infection with SARS-CoV-2 (relative risk (RR) 1.77; \( p < 0.02 \)), and severe COVID-19 (RR 1.59; \( p = 0.02 \)) [14] and mortality (RR 1.56; \( p < 0.001 \)) [10]. This shows that it is important to increase the level of 25(OH)D in COVID-19 patients [15].
The guideline for COVID-19 management from Indonesia recommends using 1,000–5,000 IU per day of vitamin D in adults [16]. Recently published studies used varied dosages. Annweiler et al. used vitamin D supplementation per month (50,000 IU/ month or 80,000 IU or 100,000 IU or 200,000 IU/2–3 months) or 800 IU/day in elderly patients with COVID-19 compared to a control group with no supplementation of vitamin D3. In the vitamin D supplementation group, they found decreasing 3-months-mortality rate compared to the control group (hazard ratio (HR) = 0.23 (95% CI: 0.09, 0.58; p < 0.002) [6]. Rastogi et al. used a higher dosage than Annweiler et al. They administered 60,000 IU of vitamin D supplementation per day for seven days in COVID-19 patients with hypovitaminosis. They stated that the group that received vitamin D supplementation had a higher percentage conversion of SARS-CoV-2 than the control group (62.5% vs 20.8%; p < 0.018) [9].

Many factors contribute to 25(OH)D levels after supplementation, such as dosage and route. Amrein et al. administered 60,000 IU of vitamin D per day for eight to ten days. This pulse-dose of vitamin D supplementation increased 25(OH)D levels from 15.65 ± 5.54 ng/mL to 88.96 ± 31.55 ng/mL [8]. Tellioglu et al. studied elderly patients with hypovitaminosis D who were administered 600,000 IU of vitamin D intramuscularly or orally. They found a significant increase in 25(OH)D levels from 11.76 ± 7.6 ng/mL to 32.72 ± 9.0 ng/mL in week 6 dan 52.34 ± 14.2 ng/mL in week 12 (p < 0.0001) in the intramuscular group. Vitamin D given orally also increased 25(OH)D levels, but not as high as intramuscularly even with the exact same dosage (from 14.87 ± 6.9 ng/mL to 47.57 ± 12.7 ng/mL at week 6 and 42.94 ± 13.4 ng/mL in week 12 (p < 0.0001). At the end of the study, 100% of the intramuscular group and 83.3% of the oral group had 25(OH)D levels of ≥ 30 ng/mL [17].

Vitamin D can be given as routine supplementation at a lower dosage or at a higher dosage over a shorter term. The most important is that vitamin D supplementation can quickly manage hypovitaminosis D to affect COVID-19 patients, especially elderly patients [10]. Usually, short-term, higher dosage is preferable due to higher patient compliance [11].

The next impending problem is how high of a 25(OH)D level is needed to achieve the immunomodulation effect. Rastogi et al. targeted a higher 25(OH)D level (> 50 ng/mL) [9], while Tellioğlu et al. targeted a 25(OH)D level ≥ 30 ng/mL [17]. Lakireddy et al. found that 25(OH)D levels of 88.96 ± 31.55 ng/mL lower inflammatory markers in COVID-19 patients with hypovitaminosis D [8]. Further research regarding target 25(OH)D levels is still needed, but with higher morbidity and mortality in COVID-19 patients with hypovitaminosis D, we suggest achieving a minimum average 25(OH)D level.

There are many mechanisms of how vitamin D affects COVID-19, such as regulating the renin-angiotensin-aldosterone system (RAS) [18]. Vitamin D reduces pulmonary permeability by modulating RAS activity and the expression of angiotensin-2 converting enzymes (ACE2) (Figure 2). SARS-CoV-2 uses ACE2 as a receptor to infect host cells and downregulating ACE2 expression, whereas ACE2 has a protective effect against inflammation. By downregulating ACE2, SARS-CoV-2 causes an inflammatory chain reaction, cytokine storm and ARDS in the host [19]. In the case of hypovitaminosis D, ACE will cause higher Angiotensin II, which leads to pulmonary vasconstriction. Pulmonary vasconstriction leads to severe COVID-19 [20, 21].

Hypovitaminosis D could be caused by decreased dietary intake and/or absorption, decreased exposure to sunlight, decreased endogenous synthesis and increased hepatic metabolism (Figure 2) [22]. The elderly tend to have lower vitamin D intake [23]. Cutaneous synthesis of vitamin D declines with age [24]. Older adults tend to have multiple medications. Medications such as phenobarbital, carbamazepine, dexamethasone, nifedipine and spironolactone induce hepatic p450 enzymes, which activate the degradation of vitamin D [25].

COVID-19 will cause higher inflammatory markers, such as D-dimer, fibrinogen and pro-inflammatory cytokines [26]. Inside the cell, vitamin D binds to nuclear vitamin D receptors (VDRs). Vitamin D has an opposing action on inflammation, as it activates the innate immune response and lowers the acquired immune response (Figure 2) [20]. Inflammatory cytokines were proven to decrease in a supplemented patient (p < 0.01) [8]. This will prevent a cytokine storm in COVID-19 patients by reducing the production of inflammatory cytokines, such as tumour necrosis factor (TNF) and interferon. Rastogi et al. found lower fibrinogen in COVID-19 patients given vitamin D supplementation compared to those without (-0.9 ng/mL vs -0.04 ng/mL; p < 0.001) [9].

Vitamin D maintains tight junctions in the cell, making it harder for the virus to infect. Another mechanism was how vitamin D affects comorbidity. Hypovitaminosis D is often correlated with a higher risk of comorbidities, like diabetes mellitus, hypertension, cardiovascular disease, respiratory disease and cancer. These co-morbidities increase the risk of mortality in COVID-19 patients [11].

Limitations of the study

There are a few limitations of this study. First, this study is a semi-systematic review. Second, the limited number of studies before did not provide establish guidelines and strong recommendations for each condition.
Conclusions
Supplementation with pulse dose vitamin D provides a clinically significant improvement, decreasing inflammatory cytokine markers in the adult population with hypovitaminosis. In the older adult population, standard vitamin D results in a reduced risk of frailty and worsening clinical features in COVID-19. As clinicians, it is important to enhance clinical awareness for recognising special populations with COVID-19 who require vitamin D supplementation above the guideline dose.

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References