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The role of serum vitamin 25(OH)D concentration in the Covid-19 pandemic in children

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Abstract

The ongoing Coronavirus disease 19 (Covid-19) pandemic and associated mortality in children led to an effort to address risk factors and develop protective measures. Observational studies in adults showed that vitamin D deficiency is associated with Covid-19 severity. The aim of this review was to summarise data regarding the role of serum vitamin 25(OH)D concentration in the severity of Covid-19 and the associated multisystem inflammatory syndrome in children (MIS-C). Many studies noted lower concentrations of vitamin 25(OH)D in children with Covid-19 compared with healthy controls; however, studies that assessed vitamin 25(OH)D suboptimal concentrations as a risk factor for Covid-19 severity were scarce. There was no high-quality evidence that vitamin 25(OH)D concentrations are associated with Covid-19 severity. Similarly, for MIS-C, a few studies with a small number of patients found that vitamin D deficiency was associated with more severe MIS-C. Vitamin D has many immunomodulatory actions and is consumed in the immunomodulatory cells, especially in infections such as the Covid-19 which is associated with increased inflammation and cytokine storm. Therefore, decreased concentrations of plasma vitamin 25(OH)D have been proposed to be the result of vitamin use by immunomodulatory cells in severe Covid-19, rather than a predisposing factor. In conclusion, the available data cannot prove that vitamin D deficiency is a risk factor for severe Covid-19 disease. More studies, of prospective design, are needed to investigate the role of this marker independently of other risk factors.

Key words: **MIS-C: Paediatric: Risk factor: SARS-CoV-2: Severity: Vitamin D**

Coronavirus disease 19 (Covid-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been declared a pandemic in March 2020[1]. The disease was considered milder in children, since most children appeared to have an asymptomatic, mild or moderate disease[2]. However, severe disease may occur, with the prevalence reported to be 2–10 % in children[2–4]. Due to severe cases and associated mortality in the paediatric population, there is a lot of discussion and research to address risk factors and develop protective measures.

Except for Covid-19 severity and associated mortality, concerns regarding children emerged also from a new clinical entity known as a multisystem inflammatory syndrome in children (MIS-C). This was considered a late presentation of Covid-19 infection and shares similar features with incomplete Kawasaki disease or toxic shock syndrome[5,6]. This complication was rare, with unknown incidence, estimated in one report to be 2 per 100 000[7]. The clinical severity of MIS-C varied, since some patients had only mild disease, while others had severe disease leading to death[8,9].

The pathophysiology of Covid-19 involves a complex interaction between the SARS-CoV-2 and the host's immune system. The virus enters cells, primarily type 2 alveolar epithelial cells, via the receptor angiotensin-converting enzyme 2 (ACE2) which results in a cytokine storm[10]. Vitamin D is a fat-soluble vitamin with many biological extraskeletal effects including both antiviral and anti-inflammatory actions[11]. The vitamin D receptor regulates the expression of more than 900 genes associated with antioxidation, and innate and adaptive immunity[12,13].

Therefore, serum vitamin 25(OH)D concentrations have been proposed as a possible predictor of severe disease. There are many observational studies in children that associated serum vitamin 25(OH)D suboptimal concentrations with increased risk for respiratory infections[14]. Following this observation, randomised trials showed that vitamin D supplementation reduced the risk of acute respiratory infections[15–17]and led to a more rapid recovery and shorter hospitalisation in children with bronchiolitis[18]. Observational studies in adults indicated that vitamin D insufficiency was associated with Covid-19 severity[19,20], and that serum vitamin 25(OH)D concentrations were an independent risk factor for Covid-19 infection and need for hospitalisation[21].

Abbreviations: ACE2, angiotensin-converting enzyme 2; Covid-19, Coronavirus disease 19; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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This review aimed to summarise data regarding the role of serum vitamin 25(OH)D concentrations in Covid-19 severity in childhood and evidence of vitamin D supplementation as a protective measure during the pandemic.

Methods

We searched the current literature for relevant studies on the role of vitamin D in the severity of paediatric Covid-19 and carried out a narrative review. A PubMed and Google Scholar search was conducted using the terms 'Covid-19', or 'SARS-CoV-2', or 'MIS-C', and 'children', or 'pediatric', and 'vitamin D' up to May 2022. In this narrative review, only papers written in English and particularly meta-analysis, systematic reviews, observational studies, and case series were included. In addition, the reference lists of the retrieved articles were carefully reviewed in the search for other relevant articles, which could have been missed during the initial searching procedure. Abstracts were not included in the paper when the full article was not available.

Vitamin D deficiency as a global problem

Vitamin D deficiency remains a global problem with a high worldwide prevalence[22]. Usually, vitamin D deficiency is defined as serum concentrations of vitamin 25(OH)D below 12 ng/ml, while insufficiency is defined as concentrations below 20 ng/ml[23]. The range of deficiency in Europe in the various teenage study populations was 12–40 %, whereas in childhood was 4–7 %[24]. Prevalence of vitamin D deficiency in children was 16 % in the USA, 7 % in South Africa, 40 % in China and 36 % in Iran[22], whereas prevalence of vitamin D insufficiency was reported in the 5·9 % of the population in the USA, 7·4 % in Canada, 13 % in Europe and in > 20 % of the population in India, Tunisia, Pakistan and Afghanistan[25].

Pandemic, accompanied by many restrictions, such as home confinement and school closures, led to the deterioration of this problem by having a significant adverse impact on serum vitamin 25(OH)D concentrations. Many studies noted decreased vitamin 25(OH)D concentrations in children during the pandemic compared with the era before, since the main source of vitamin D is skin synthesis after sunlight exposure[26–30]. This was observed in all ages, from infants and toddlers[29]to school-aged children and adolescents[26]. In a study of 303 infants and toddlers in Hong Kong, a decreasing trend was observed in the months post-outbreak at a monthly decline rate of –2·53 ng/ml in serum vitamin 25(OH)D concentrations, and this was stronger among younger infants (2–6 months old)[29]. During the pandemic, there was also no seasonal variability in serum vitamin 25(OH)D concentrations[28].

Serum vitamin 25(OH)D concentrations and Covid-19 severity

Studies in adults, mostly observational and population-based, indicated that vitamin D insufficiency was associated with Covid-19 severity[19,20], and that serum vitamin 25(OH)D concentrations were an independent risk factor for Covid-19 infection and need for hospitalisation[21]. A meta-analysis of twenty-one studies found that patients with concentrations of vitamin 25(OH)D below 20 ng/ml had 2·42 times increased risk to have severe Covid-19, but vitamin 25(OH)D concentrations had no effect on mortality[31]. On the other hand, a meta-analysis of thirty-one observational studies concluded that available evidence to date may be showing a weak association between low concentrations of vitamin 25(OH)D and Covid-19 outcomes, yet a statistically significant relationship could not be established[32]. So, even if there is evidence of an association between serum vitamin 25(OH)D concentrations and Covid-19 severity, data are still conflicting in adults.

Regarding children, several retrospective studies noted that those with Covid-19 had lower serum vitamin 25(OH)D concentrations compared with healthy children (Table 1)[33–36]. A meta-analysis of Shah *et al.* showed a pooled prevalence of vitamin D

Table 1. Studies assessing serum vitamin 25(OH)D concentrations in children with Covid-19

Study	Study type	Country, time period	Population	Age, years (range, mean)		Primary outcome
Bayramoglu E, *et al.*[38]	Retrospective	Turkey, March–May 2020	103	1–17	12·2	Children with moderate-to-severe Covid-19 had the lowest median vitamin D levels Vitamin D deficiency was an independent predictor of moderate-to-severe disease
Alpcan A, *et al.*[33]	Retrospective	Turkey, May–December 2020	75 children	1–18	10·7	Vitamin D levels were significantly lower in Covid-19 patients No children had severe disease vitamin D level was a risk factor for respiratory distress
Yilmaz K and Sen V[36]	Retrospective	Turkey, March–May 2020	40 patients	1–18	8·5	Lower vitamin D levels in children with Covid-19 No difference in disease severity according to vitamin D levels
Katz J, *et al.*[34]	Retrospective	USA, October 2015–June 2020	87 patients	Children and adults		Patients with vitamin D deficiency were five times more likely to be infected with Covid-19
Olive-Cirera G, *et al.*[35]	Retrospective	Spain, March 2020–March 2021	153	8–16	13	Low levels of vitamin D were risk factor for Covid-19

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deficiency of 45·91 % in Covid-19 patients[37]. This meta-analysis of retrospective studies and case series also showed that children with vitamin D deficiency have a greater risk for Covid-19 infection compared with children with optimal levels[37]. Katz *et al.*, in a retrospective study of patients' registry, quantified this observation and found that the risk of Covid-19 is five times higher in children with vitamin D deficiency, after adjustment for co-morbidities and demographic covariates[34].

However, most of the available retrospective studies did not associate vitamin D insufficiency or deficiency with infection severity, since the severe disease was rare in the population of the studies and no patients required admission to intensive care. Only in two studies, serum vitamin 25(OH)D concentrations were correlated with disease severity. Bayramoglu *et al.* assessed in their study vitamin 25(OH)D concentrations in 103 children with Covid-19 and found that levels were significantly lower in the moderate-to-severe disease compared with children with mild disease, while vitamin D deficiency was found to be an independent predictor of severe clinical course. In this study, moderate-to-severe disease was defined as pneumonia in hospitalised children. Interestingly, children with severe disease had a mean vitamin 25(OH)D concentration almost 40 % lower than those who had asymptomatic disease. This association was observed when there was a deficiency of vitamin 25(OH)D concentrations (<12 ng/ml) but not an insufficiency (12–20 ng/ml)[38]. In this study, children with co-morbidities were excluded and so were infants due to routine vitamin D supplementation in this age group. This was a single-centre study and due to its retrospective design, a cause–effect relationship cannot be fully established. Furthermore, in this study, other confounding factors, such as obesity and anthropometric measures affecting vitamin 25(OH)D concentrations, were not taken into account.

On the other hand, a smaller study of forty children with Covid-19 did not find a statistically significant difference in severity and length of hospitalisation between children with vitamin 25(OH)D concentrations < 20 ng/ml[36]. However, it should be noted that this study had a smaller population, only two children had severe disease, defined as dyspnea and central cyanosis, and there was no subgroup analysis for children with deficient concentrations (< 12 ng/ml).

Shah *et al.* included these two studies in their analysis and concluded that in infected paediatric patients, low serum vitamin 25(OH)D concentrations increased the risk of severe disease (OR –5·5; 95 % CI 1·560, 19·515; $P = 0·008$)[37]. However, this evidence arises only from two single-centre studies of retrospective design, with a small total number of subjects. Thus, more accurate conclusions should be drawn from larger randomised controlled trials.

In recent studies, there was also an effort to associate vitamin 25(OH)D concentrations with symptoms and laboratory findings of Covid-19. Plasma vitamin 25(OH)D concentrations negatively correlated with levels of inflammatory markers (C-reactive protein and fibrinogen)[38] and lower lymphocyte count[33,38]. The vitamin D-deficient group of children had the lowest lymphocyte levels[38]. Lymphopenia is an indicator of severe disease[39], and it has been shown that the lowest lymphocyte counts are reached when the inflammatory cytokine levels are at the highest levels[40]. The SARS-CoV-2 may directly infect lymphocytes via the ACE2 receptor[41], while in critical disease, a systemic increase in cytokines and inflammatory mediators may result in marked lymphocytic apoptosis[42–44].

Regarding fever, the available data are conflicting. In a retrospective study of seventy-five children from Turkey, there was no correlation between fever and serum vitamin 25(OH)D concentrations in Covid-19[33], while in another study of forty patients with Covid-19 fever was significantly higher when concentrations of vitamin 25(OH)D were lower[36].

In conclusion, available data are scarce and there is no high-quality evidence that vitamin 25(OH)D concentrations are associated with Covid-19 severity. There are several retrospective studies with a small number of patients, and most of them did not assess vitamin 25(OH)D concentrations as an independent predictor of disease severity[33–36].

Serum vitamin 25(OH)D concentrations and multisystem inflammatory syndrome in children severity

MIS-C is an uncommon complication of Covid-19, yet with a disease course that can be quite severe, so risk factors and predictors of severe disease should be addressed[8]. In a retrospective single-centre study of thirty-one patients under 18 years old with MIS-C from the USA, ten patients had severe vitamin D deficiency, and these patients had longer intensive care unit and hospitalisation length, as well as increased risk for cardiac involvement. Ninety percent of patients with severe vitamin D deficiency had severe disease, which was defined as patients requiring inotropic support, mechanical ventilation, veno-arterial extracorporeal membrane oxygenation or disease resulting in death[45]. Nevertheless, the study population was small to allow for proper testing of other possible confounding factors of severe disease.

In another study of eighteen children with MIS-C and no notable co-morbidities, 89 % of children had suboptimal vitamin 25(OH)D concentrations (72 % deficient and 17 % insufficient) and most children required intensive care[46]. In this study, children needing intensive care unit support had lower serum vitamin 25(OH)D concentrations than those not requiring intensive care. Nevertheless, the median differences in the two groups of vitamin25(OH)D concentrations were small (18·2 *v.* 23·5 nmol/l). The authors proposed vitamin D supplementation all year round, especially for children at high risk for vitamin D deficiency. Finally, a safe conclusion regarding the role of vitamin D in MIS-C severity cannot be made, since available data are only from two single-centre, retrospective studies including a small number of patients.

Vitamin D as an immune regulator

Regarding Covid-19, vitamin D reduces the apoptosis of type II pneumonocytes and stimulates surfactant synthesis in these cells, thus preventing the risk of acute respiratory syndrome[47]. Furthermore, vitamin D modulates both innate and adaptive immunity[11,48]. Regarding innate immunity, vitamin $1,25(OH)_2D$ induces the production of antimicrobial peptides such as cathelicidin LL-37 and defensins by macrophages and respiratory epithelial cells[48–51]. Vitamin D also

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modulates adaptive immunity through suppressing T lymphocyte proliferation and altering the activity of different types of T-helper cells. A shift from type 1 T-helper cells and type 17 T-helper cells profile to type 2 T-helper cells profile is promoted leading to a decrease in the production of pro-inflammatory cytokines and thus reduction of the cytokine storm[48,51,52].

SARS-CoV-2 enters the cells via the ACE2 resulting in the down-regulation of ACE2 in the lungs and accumulation of angiotensin II. This leads to inflammation and vasoconstriction and thus the complications accompanying Covid-19.Vitamin 1,25(OH)2D regulates the renin-angiotensin-aldosterone system by inhibiting renin and inducing the expression of ACE2 in the lungs[48,51].

On the other hand, severe infections such as Covid-19 can lead to the consumption of vitamin D by the immunomodulatory cells. The utilisation of vitamin D is faster than its production, and this may lead to vitamin D deficiency. Therefore, decreased concentrations of plasma vitamin 25(OH)D have been proposed to be the end result of vitamin use by immunomodulatory cells in severe Covid-19, rather than a separate predisposing factor[53].

MIS-C is the result of an altered and exaggerated immune response against SARS-CoV-2, in which the level of inflammation outweighs the inflammation observed in Covid-19[54]. The cytokines that are mostly involved in the acute phase are IL-1β, IL-6, IL-8, IL-10, IL-17, IFN-γ, and differential T and B cell subset lymphopenia[55,56]. Vitamin D may have an impact on MIS-C severity mainly through its anti-inflammatory actions. As described above, vitamin 1,25$(OH)_2$D alters the activity of different types of T-helper cells. A shift from type 1 T-helper cells and type 17 T-helper cells profile to type 2 T-helper cells profile is promoted leading to a decrease in the production of pro-inflammatory cytokines and reduction of the cytokine storm[11,53,57].

The role of vitamin D supplementation

There are no available studies assessing the effect of vitamin D supplementation in children with Covid-19. Recent systematic reviews and meta-analyses of adult observational studies concluded that current evidence is insufficient to prove a benefit of vitamin D supplementation in Covid-19[58]. Regarding other infections, previous meta-analyses of randomised controlled trials have shown an effect of vitamin D supplementation in preventing acute respiratory tract infection both in children and adults[17,59]. Daily administration of 400–1000 µg of vitamin D for up to 12 months reduced the risk of acute respiratory infection[17]. Children and adults that had baseline vitamin 25(OH)D concentrations lower than 10 ng/ml had the most benefit in protection from acute respiratory infections from vitamin D supplementation[59]. Therefore, the role of vitamin D supplementation should be further studied during the pandemic in children, in randomised controlled studies, for not only its efficacy but also the optimal dose and duration of supplementation to be established.

Conclusion

In conclusion, although there is a lot of discussion regarding the role of vitamin D in the pandemic, the evidence that vitamin D is a risk factor for severe disease in children is of poor quality. Furthermore, it is unclear whether vitamin D is a risk factor, or whether it is an epiphenomenon of severe disease, since vitamin D may be consumed during severe disease process. More studies, of prospective design, are needed to assess the role of this marker independently of other risk factors. The efficacy of vitamin D supplementation should also be assessed in randomised controlled trials. Although vitamin D administration is relatively free of side effects, the optimal dose and duration of its administration in order to have a preventive effect should also be clarified.

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