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REVIEW
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Exploring the Therapeutic Potential of Vitamin D in Kawasaki Disease and Its Interplay with the COVID-19

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ABSTRACT

Objective: Several studies have reported outbreaks of Kawasaki disease among children amid the coronavirus disease 2019 (COVID-19) pandemic. Vitamin D possesses high utility in modulating the immune system to repair and prevent severe inflammation in COVID-19. This study aims to explore the association between Kawasaki disease and vitamin D levels in pediatric patients and describe the potential role of vitamin D in promoting recovery and preventing complications associated with Kawasaki disease in pediatric patients with COVID-19.

Materials and Methods: The association between Kawasaki disease and vitamin D was explored adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, utilizing databases such as PubMed, Google Scholar, and ScienceDirect. The association between COVID-19 and Kawasaki disease was also assessed by reviewing relevant literature.

Results: Most studies indicated that patients with Kawasaki disease had lower vitamin D levels. Vitamin D supplementation was also found to be deficient in the pediatric population with Kawasaki disease. Inflammation of the endothelium, cytokine storms, and endothelial dysfunction in patients suffering from COVID-19 may contribute to the development of Kawasaki disease. Vitamin D is believed to have protective potential for Kawasaki disease outcomes by modulating the inflammatory response.

Conclusion: Administering vitamin D to pediatric patients with viral infections like COVID-19 is expected to accelerate clinical improvement and prevent complications from Kawasaki disease.

Keywords: Child health, COVID-19, Kawasaki disease, vitamin D

INTRODUCTION

During the last 4 years, the coronavirus disease 2019 (COVID-19) pandemic has significantly affected public health globally, impacting various age groups, including pediatric patients.[1,2] At the beginning of the pandemic, there was a rapid increase in COVID-19 cases among children, although it subsequently decreased gradually. Surprisingly, several recent studies have reported outbreaks of Kawasaki disease in children affected by the COVID-19 pandemic.[3,4] Kawasaki disease, first identified by Japanese pediatrician Dr. Tomisaku Kawasaki, is characterized as a lymph node mucocutaneous syndrome. It is diagnosed when a child presents with a fever lasting a minimum of 5 days and displays 4 or more of the following 5 symptoms: changes in the limbs, rash, conjunctivitis, oral changes, and cervical lymphadenopathy.[5] Kawasaki disease has been frequently mentioned in various countries worldwide, with offspring of Japanese descent tending to have the highest risk.[6,7]

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Kawasaki illness was strongly associated with COVID-19 "after effect" in the pediatric population by the discovery of its elevated occurrence after the COVID-19 pandemic. Moreover, it has been observed that a majority of children with Kawasaki disease experience a severe form of the illness.[3] Despite numerous studies investigating its cause, the exact etiology of Kawasaki disease remains unclear. One of the currently proposed etiological hypotheses is infectious agents in susceptible children.[6] Kawasaki disease is characterized as vasculitis in children, with its primary complication being coronary artery aneurysm. In addition, patients with a history of Kawasaki disease with coronary artery aneurysms can exhibit increased carotid intima-media thickening as a marker of extracardiac vasculitis.[8] Therefore, further research into Kawasaki disease prevention strategies in the pediatric population is still needed.[9]

Treatment of Kawasaki's disease in the acute phase aims to reduce inflammation and arterial damage and to prevent thrombosis in those with coronary artery abnormalities.[5] The primary treatment for Kawasaki disease includes intravenous immunoglobulin (IVIG) and aspirin. Intravenous immunoglobulin is administered along with high-dose aspirin until the patient does not have a fever for more than 48 h. Aspirin is thought to control platelet activity by reducing inflammation and averting thrombosis, although there is no proof that aspirin truly stops coronary artery aneurysms from developing.[10] However, the administration of aspirin also has a higher risk of Reye's syndrome in children if they are infected with influenza or varicella.[5] Corticosteroids have also been proposed as part of the initial therapy for Kawasaki disease due to their ability to reduce the risk of developing heart disease. However, research results have remained inconsistent because they indicate the possibility of resistance to IVIG.[11]

Several studies have shown that vitamin D possesses high utility to modulate the immune system in repairing and preventing severe inflammation in COVID-19 patients.[12] Similarly, studies have indicated lower levels of vitamin D in patients with Kawasaki disease, mirroring trends seen in COVID-19 patients.[13] Administering vitamin D to pediatric patients with COVID-19 and those at risk of Kawasaki disease could potentially improve outcomes. This study aims to collect evidence on the association between vitamin D levels and Kawasaki disease, exploring possible underlying mechanisms and assessing the potential benefits of vitamin D supplementation in pediatric COVID-19 patients.

MATERIALS AND METHODS

Data Sources

A computerized literature search was conducted across multiple databases, including "ScienceDirect," "PubMed," and "Google Scholar." The search strategy employed keywords such as "vitamin D" or "Cholecalciferol" or "Hydroxycholecalciferols" or "Calcifediol" or "Dihydroxycholecalciferols" or "24,25-Dihydroxyvitamin D3 Calcitriol" or "Ergocalciferol" or "25-Hydroxyvitamin D2" or "Dihydrotachysterol" and "Kawasaki disease" or "Kawasaki syndrome" or "Lymph Node Syndrome, Mucocutaneous" or "Mucocutaneous Lymph Node Syndrome." The search was conducted up to March 2023.

Study Selection

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines[14] and followed the Cochrane Handbook for Systematic Reviews of Interventions.[15] Search results from each database were collated and managed collectively using Google Sheets (https://docs.google.com/spreadsheets/) (Google LLC, Mountain View, CA, USA). After removing duplicate records, the remaining articles underwent initial screening based on their titles and abstracts. Articles passing this stage were retrieved for full-text evaluation. Subsequently, all studies were rigorously assessed against predefined eligibility criteria. The literature searches and study selection processes were conducted by VIS, YOW, and FMA. Any discrepancies were resolved through consensus among the team members.

Eligibility Criteria

We employed the Population, Intervention, Comparison, Outcome (PICO) framework (Table 1) recommended for systematic reviews to define and establish our eligibility criteria.[16] Studies were considered for inclusion in the systematic review if they met the following criteria: (1) the study population comprised children diagnosed with Kawasaki disease; (2) children aged 1 month to 17 years old; (3) they measured vitamin D levels; (4) included a comparison group; and (5) observational study designs (cross-sectional, cohort, and case–control). Exclusion criteria encompassed: (1) studies with irrelevant titles or abstracts; (2) full texts that could not be retrieved; and (3) study types such as review articles, case reports, case series, or conference abstracts.

Data Extraction and Quality Assessment

In the data extraction process, 2 independent reviewers (YOW and FMA) extracted data from all included studies using a standardized template. After the initial extraction, the 2 data sets were compared to identify any discrepancies by a third reviewer (VIS). A third reviewer adjudicated the differences, and a final decision was made based on pre-established criteria. The extracted data included the first author's name and year of publication, study location (country), study design, sample size, number of female participants, age range, and study outcomes. The characteristics and outcomes extracted from each included study were presented descriptively in a table format.

The methodological quality assessment of the included studies was performed using the Newcastle–Ottawa Scale (NOS) tool.[17] The NOS tool evaluates studies across 3 domains: selection, comparability, and exposure, assessing the risk of bias and concerns regarding applicability using specific signaling questions. Studies were categorized as having good, fair, or

Table 1. PICO Framework

Components of PICO	Definition
Population	Pediatric patients
Intervention (Exposure)	Kawasaki disease
Comparison	Control group
Outcome	Vitamin D level

PICO, population, intervention, comparison, and outcome

poor quality based on stars received in the selection, comparability, and exposure domains.

RESULTS

Overview of Study Selection Process

The PRISMA flow diagram (Figure 1) outlines the study selection process. Initially, searches across 3 databases yielded 1044 results. Automation tools removed 716 records, and 27 duplicates were identified. After screening titles and abstracts, 261 and 14 records were excluded, respectively. A thorough review of the remaining 26 studies led to the exclusion of 19 studies: not in English (n = 1), incorrect study type (n = 3), not involving vitamin D supplementation (n = 10), and lacking relevant outcomes (n = 5). Ultimately, 7 studies met the eligibility criteria and were included in the analysis.

Association of Vitamin D Level with Kawasaki Disease

Table 2 summarized the characteristics and main outcomes of included studies. A total of 7 studies yielded 1721 children (range age: 4 months-6.5 years). Most studies were conducted in China, with all studies applying a case–control design. Studies by Meyer et al,[18] Stagi et al,[13] Chen et al,[19] and Zhang et al[20] found lower vitamin D supplementation or vitamin D levels in the pediatric population with Kawasaki disease. The study by Chen et al[21] found higher serum 25-(OH)D3 in the acute phase of Kawasaki disease patients than in the control. Qi et al[22] found a higher vitamin D receptor, P65 pathway, and extracellular signal-regulated kinase in patients with Kawasaki disease. In the management of Kawasaki disease treatment, it may be useful to look at the vitamin D level if it is accessible and replace vitamin D if there is a low level.

The overall detailed risk of bias evaluation for each study is summarized in Table 3. According to the NOS tool, 1 study was rated 3 stars in the selection domain, and 2 studies received only got 1 star in the comparability domain. Meanwhile, 2 studies were rated 2 stars in the exposure domains. However, all the studies have good quality overall.

DISCUSSION

Association of Vitamin D with Kawasaki Disease

Most studies suggest that children diagnosed with Kawasaki disease commonly have reduced vitamin D levels, especially in cases involving coronary artery abnormalities. In the included studies, the standardization of vitamin D level measurements was done using the ELISA method for objective measurement. The evaluation of the duration of vitamin D supplementation in pediatric Kawasaki disease patients and controls has also been adjusted to the same dose of 400-500 IU/day during the first

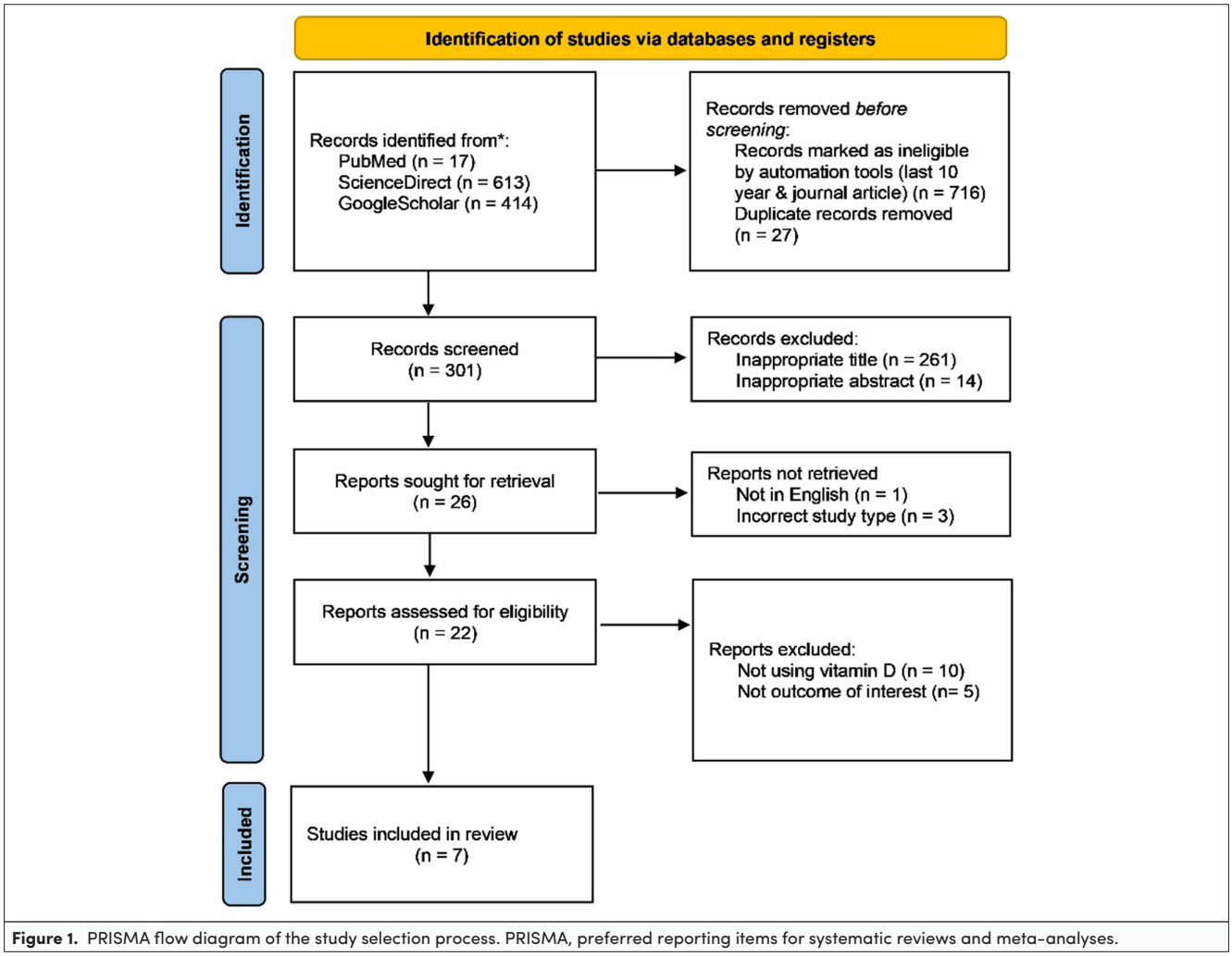

Figure 1. PRISMA flow diagram of the study selection process. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Table 2. Study Assessed Levels of Vitamin D in Kawasaki Disease Patients

Author	Location	Study Design	Sample Size		Age	Outcomes
			Case (Female)	Control (Female)		
Meyer et al., 2019[18]	Germany	Case–control	308 (114)	321 (137)	6.5 year	Shorter duration of vitamin D supplementation in KD than control (OR0.964; 95% CI: 0.931-0.998; *P* = .039) Lower regularity of vitamin D supplementation in KD than control (OR 0.559; 95%CI:0.319-0.980; *P* = .042)
Chen et al., 2014[21]	China	Case–control	26 (6)*9 (3)**	Febrile 23 (12) Healthy 30 (14)	4 months-4 years	Higher serum 25-(OH)D3 in healthy than febrile group (44.1±30.2 vs 27.9±20.2 ng/mL; *P* = .025) Lower serum 25-(OH)D3 in healthy than NCALs group (44.1±30.2 vs 49.2±23.8 ng/mL; *P*=.49) Lower serum 25-(OH)D3 in NCALs than CALs group (49.2±23.8 vs 83.9±26.3 ng/mL; *P* = .001)
Chen et al., 2014[19]	China	Case–control	35 (9)	Febrile 25 Healthy 25	N/A	Higher serum 25-(OH)D3 in healthy than febrile group (*P* = .025) Higher serum 25-(OH)D3 in healthy than KD group (*P* =.00)
Zhang et al., 2016[20]	China	Case–control	179* 63*	Febrile 40 Healthy 40	N/A	Higher serum 25-(OH)D3 in healthy than febrile group (40 ± 10 vs 22 ± 5 ng/mL; *P* < .05) Higher serum 25-(OH)D3 in healthy than NCALs group (40 ± 10 vs 22 ± 5 ng/mL; *P* < .05) Higher serum 25-(OH)D3 in healthy or febrile or NCALs groups than CALs group (*P* < .01) Positive correlation between serum 25-(OH)D3 level and serum IL-6 in KD group (*P* = .000)
An et al., 2016[23]	China	Case–control	45 (21)	Febrile 43 (21) Healthy 46 (24)	3.1 ± 2.9 years	Lower serum 25-(OH)D3 in healthy or febrile than KD group (*P* < .05) Lower serum IL-6 in healthy or febrile than KD group (*P* < .05)
Qi et al., 2017[22]	China	Case–control	30	Febrile 60 Healthy 60	N/A	Higher VDR expression in KD than febrile and normal group Higher P-ERK expression in KD than febrile and normal group Expression of *P53* only in KD
Stagi et al., 2016[13]	Italy	Case–control	79 (21)	234 (85)	4.6 ± 1.9 years	Higher serum 25-(OH)D3 in control than KD group (*P* < .001)

**CALs, coronary arterial lesions; IL-6, interleukin-6; KD, Kawasaki disease; mo, months; *NCALs, non-coronary arterial lesions; P-ERK, P65 pathway and extracellular signal-regulated kinase; VDR, vitamin D receptor; vs, versus; yr, years.Quality Assessment of Included Studies

year of life. Only a single study has reported contrary results, but the reason remains unexplained.[23] Low vitamin D levels also correlate with the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, and hemoglobin levels, as an indicator of high inflammation process in Kawasaki disease. Lack of anti-inflammatory and immunomodulatory effects from vitamin D can lead to a higher inflammation process in Kawasaki disease.[24]

Vitamin D can suppress the expression of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), which are involved in the development of Kawasaki disease by inhibiting the activation of nuclear factor kappa B (NF-κB).[24] NF-κB activity on monocytes/macrophages and T lymphocytes is significantly elevated in children with acute Kawasaki disease. More specifically, activation of NF-κB is known to be higher on $CD14^+$ cells at the acute stage than $CD3^+$ cells at the subacute and convalescent stage.[25] Through the inhibition of NF-κB synthesis by vitamin D, T-cell activation will decrease, thus reducing autoimmune responses.

However, a previous observational study involving 30 children with the acute phase of Kawasaki disease provided contrasting results.[21] During the acute phase of Kawasaki disease, the body undergoes a significant inflammatory response that possibly influences the conversion of vitamin D to its active form. The differences in genetic, environmental, and nutritional factors could contribute to the variability in these findings.[21] The exact pathophysiological mechanism behind this elevation remains to be clarified.

Vitamin D administration has not been able to suppress cytokine secretion through NF-κB, a cytokine-induced gene expression regulator and apoptotic regulator.[22] In addition, it has been reported that *P53* gene inactivation contributes to the apoptotic process. All of these factors cause the failure of apoptosis, causing T cells to continue to proliferate and differentiate, leading to an immune imbalance in the body. *In vitro* administration of 1,25-(OH)2D3 also found that this intervention is able to inhibit the activation of the ERK1/2 signaling pathway, reactivate the *P53* gene significantly, and finally inhibit T cell hyperplasia.[22]

Table 3. Newcastle-Ottawa Scale Assessment for Included Studies

Author	Selection	Comparability	Exposure	Overall
Meyer et al., 2019[18]	4	2	2	Good
Chen et al., 2014[21]	4	2	3	Good
Chen et al., 2014[19]	4	1	3	Good
Zhang et al., 2016[20]	4	1	3	Good
An et al., 2016[23]	4	2	3	Good
Qi et al., 2017[22]	4	1	2	Good
Stagi et al., 2016[13]	4	1	3	Good

In a prior study, it was noted that 1,25-(OH)2D3 could effectively reduce TNF-induced surface expression of VCAM-1 and IL-8 production in human coronary artery endothelial cells. These findings propose the potential use of 1,25-(OH)2D_3 as a supplementary therapy to regulate the inflammatory response during vasculitis in Kawasaki disease. Furthermore, serum levels of 25-(OH)D3 during the acute phase of Kawasaki disease might serve as a predictor for coronary artery lesions in children.[21]

The hypothesis linking the stimulator of interferon genes (STING) pathway to Kawasaki disease pathogenesis supports using vitamin D as adjunctive therapy.[26] Overactivation of the STING pathway can exacerbate the severity of Kawasaki disease and cause delayed aneurysms.[27] Calcitriol (1,25-(OH)2D_3) is known to inhibit the cGAS/STING/IFN cascade pathway, which is implicated in the development of Kawasaki disease.[28] Additionally, vitamin D levels are considered a potential predictor of IVIG resistance during the treatment of Kawasaki disease patients. The incidence of IVIG resistance was significantly higher in patients with vitamin D levels under 20 ng/mL.[29] However, the mechanism of vitamin D against IVIG resistance is still not fully understood.

Reports have indicated that adding 1-alpha, 25-dihydroxyvitamin D3 as therapy demonstrates anti-inflammatory properties and the ability to modulate the immune response in Kawasaki disease vasculitis.[13,18] The expression of Vitamin D receptor (VDR) in T cells was found to be higher in KD patients compared to febrile children with respiratory tract infections and healthy children.[20,21] The heightened activity of T cells in KD patients may stimulate the production of 25-(OH)D3. Consequently, the more pronounced inflammatory response seen in patients with coronary artery lesions (CAL) might induce greater VDR expression, thereby potentially increasing levels of 25-(OH)D3.[22]

Association of COVID-19 with Kawasaki Disease

Although some evidence has linked the development of a multisystem inflammatory syndrome with an immunologic reaction following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the mechanism of this immune response is still unclear.[30,31] Respiratory tract viral infections, particularly rhinoviruses, enteroviruses, and coronaviruses, have long been associated with Kawasaki disease.[32] Cytokines, pro-inflammatory agents, play a crucial role in the pathogenesis of COVID-19, causing the accumulation of inflammation in the endothelium. This inflammation changes endothelial function from a homeostatic to a protective state.[33] Moreover, an impaired immune response, particularly an uncontrolled natural inflammatory response, contributes to a cytokine storm in COVID-19 patients, potentially increasing the likelihood of Kawasaki disease development in these individuals, as shown in Figure 2.[34]

Another hypothesis suggests that the cytokine storm underlying Kawasaki disease is due to multiorgan autoimmune interactions.[35] Mucous cells, cardiomyocytes, and endothelium in Kawasaki disease patients present autoantigens in autoimmune occurrence. Antigen-antibody interaction triggers the formation of immune complexes by the expression of Fcγ receptors on neutrophils and monocytes. The binding of antibodies to Fcγ receptors promotes more cytokine secretion.[36,37]

According to the clinical management guideline, COVID-19 patients diagnosed with Kawasaki disease receive treatment involving IVIG and anti-inflammatory agents.[5,9] Some patients with COVID-19 and Kawasaki disease may require additional treatment, particularly steroids. Patients with Kawasaki disease may develop vasculitis or coronary artery aneurysm, whose rupture will induce the formation of thrombosis and myocardial infarction.[5,8] Therefore, Kawasaki patients with hemodynamic failure/instability are highly recommended to be admitted into the intensive care unit for hemodynamic management.[32]

Association of Vitamin D with COVID-19

Vitamin D is known to have the potential to regulate natural and adaptive immune responses. Vitamin D derivatives, either 25-(OH)D3 or 1,25-(OH)2D3, have enhanced autophagy through several pathways and upregulation of intracellular Ca and NO that mediate antiviral activity.[12] Through the hCAP18/

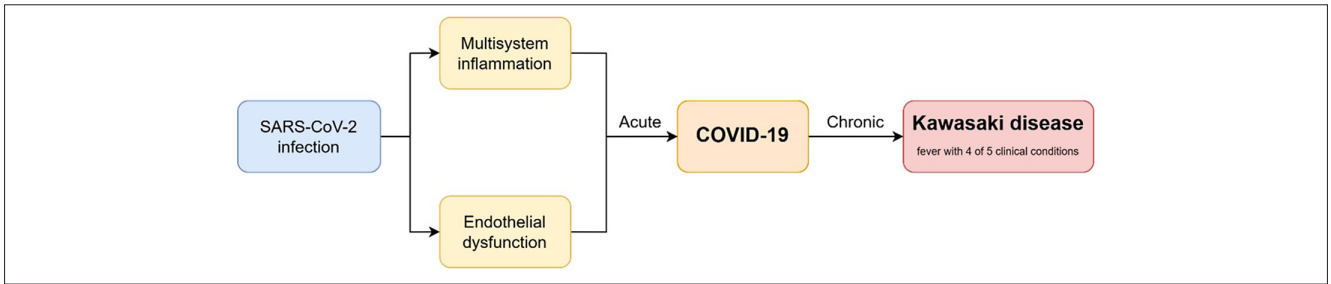

Figure 2. Relation between Kawasaki disease and COVID-19. COVID-19, corona virus disease 2019; SARS-COV-2, severe acute respiratory syndrome-corona virus-2.

LL-37-mediated pathway, 1,25-(OH)2D3 triggers autophagosome and auto phagolysosome maturation.[38] Several pathways that regulate Bcl-2, the mammalian target of rapamycin (mTOR), the class III phosphatidylinositol 3-kinase complex, and cathelicidin production are targets for autophagy stimulation by 1,25-(OH)2D3.[39] Vitamin D has been demonstrated to induce autophagy, which can reduce infection with various viruses. However, its immunomodulatory effect on viral infection is understood to be somewhat restricted. Furthermore, vitamin D modulates adaptive immunity by restraining the maturation of dendritic cells, which in turn hinders the presentation of antigens to T cells. This action shifts the pro-inflammatory profile of TH1 and Th17 cells towards a more anti-inflammatory profile dominated by Th2 and T regulatory cells, thereby mitigating the inflammatory process.[40]

The airway epithelium expresses both the *CYP27B1* gene, 1,25-(OH)2D3, and the vitamin D receptor. In infectious pathogens, alveolar macrophages are prompted to upregulate both the *CYP27B1* gene and the vitamin D receptor. Immune activation triggers increased local production of 1,25-(OH)2D3, which aids in viral neutralization and clearance while also regulating the ensuing pro-inflammatory response. However, the specific application of this process to SARS-CoV-2 has not been conclusively demonstrated.

The mechanism of 1,25-(OH)2D3 against COVID-19 infection via the renin–angiotensin–aldosterone system (RAAS) is shown in Figure 3. Angiotensin-converting enzyme-2 (ACE-2), the specific receptor for COVID-19, is regulated through the activation of 1,25-(OH)2D3 or calcitriol. 1,25-(OH)2D3, as a negative modulator of the RAAS, inhibits renin secretion and stimulates ACE-2.[41] Inhibition of ACE-2 results in elevated levels of angiotensin II and reduced levels of angiotensin-(1,7).[42] Angiotensin II acts primarily as a vascular vasoconstrictor. However, when there is a decrease in angiotensin (1-7), angiotensin II has pro-inflammatory, pro-fibrotic, pro-oxidant, fibrosis, proliferation, inflammation, and oxidative stress effects that trigger SARS-CoV disease.[41,43] In contrast, the administration of 1,25-(OH)2D3 triggers an increase in angiotensin (1-7), which has the opposite effect on angiotensin II.[44] Angiotensin (1-7) has anti-inflammatory, anti-fibrotic, anti-oxidant, vasodilating, and vascular protective effects.[43]

In a preliminary clinical trial, COVID-19 patients were given high doses of calcifediol, an ingredient that can raise 25-(OH) D3 levels. The results show that it was able to significantly reduce the number of patients requiring intensive care unit (ICU) admission. Calcifediol appears to be able to reduce the severity of COVID-19. However, large clinical trials still need to be conducted to support this finding.[45]

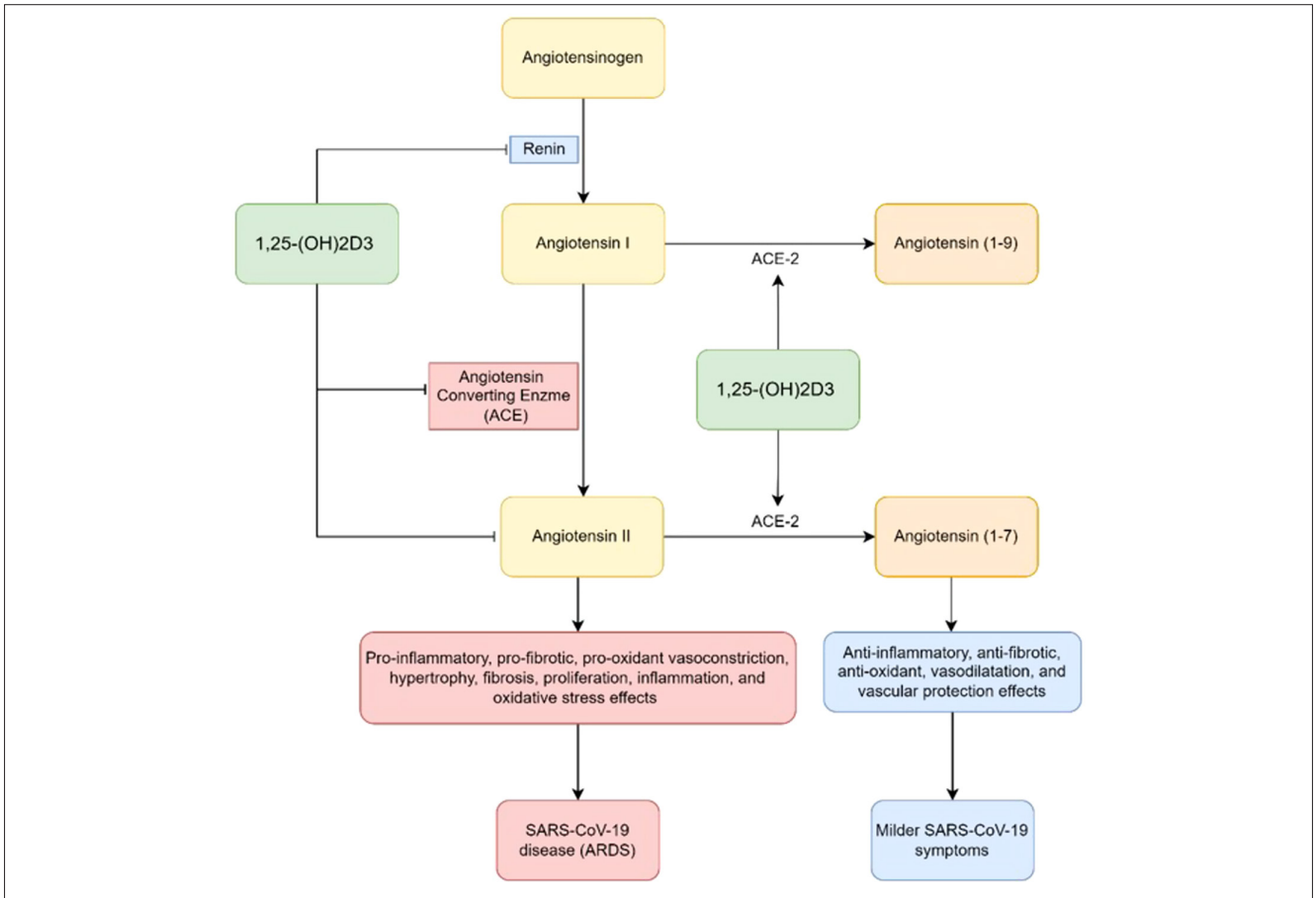

Figure 3. Mechanism of 1,25-(OH)2D3 against COVID-19 infection via the RAAS. ACE-2, angiotensin-converting enzyme-2; ARDS, acute respiratory distress syndrome; SARS-COV-19, severe acute respiratory syndrome-coronavirus-2019.

A comparative study with a total of 191779 patients found that the SARS-CoV-2 positivity rate was robust and significant contrast to levels of 25-(OH)D3.[46] Vitamin D deficiency was found to be expected in COVID-19 patients but was not associated with disease outcome.[47] In contrast, an observational study conducted within the Indian population indicated a correlation between lower vitamin D levels and increased mortality.[48] The variability in research findings concerning vitamin D levels and the incidence of COVID-19 across multiple studies underscores the necessity for cohort studies or randomized controlled trials to establish a conclusive understanding.

However, this current study has several limitations. The majority of included studies remain observational in nature. Kawasaki disease is primarily diagnosed clinically, and specific therapies for this condition are relatively under-researched. Some confounding factors could not be fully controlled, such as daily intake and secondary infections in children. Moreover, this study did not involve children with malnutrition, malabsorption disorders, and comorbidities that could affect the patient's recovery prognosis. In the quality assessment of the studies, all studies were evaluated and found to have sufficient quality to be included in this review. The authors strongly recommend conducting experimental research and further clinical trials to thoroughly assess the potential role of vitamin D in managing pediatric patients with COVID-19.

CONCLUSION

The majority of studies have demonstrated lower vitamin D levels in patients with Kawasaki disease. Vitamin D is recognized for its immune-regulatory and antiviral properties, which could potentially support clinical outcomes and serve as an adjunct therapy for both COVID-19 and Kawasaki disease. Further experimental research and clinical trials are needed to assess the potential benefits of vitamin D supplementation in pediatric patients with viral infections.

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