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Vitamin D and morbidity in children with Multisystem inflammatory syndrome related to Covid-19☆

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ABSTRACT

Background: Multisystem inflammatory syndrome (MIS-C) is a clinical presentation reported in children related to Coronavirus-19 infection who present with a toxic shock like syndrome. Vitamin D deficiency has been postulated to play a role with severity of coronavirus infection in adult patients and other viral respiratory infections.
Objective: This study aims to investigate if severe vitamin D deficiency was associated with increased disease severity and cardiac involvement in MIS-C.
Methods: This is a retrospective and single center study. We included hospitalized patients less than 18 years of age with diagnosis of MIS-C between March and July 2020. Severe vitamin D deficiency was defined as 25-OH vitamin D level < 10 ng/ml within 48 h of admission. The composite outcome severe disease included patients requiring inotropes, mechanical ventilation, and extracorporeal membrane oxygenation.
Results: Of the 31 patients with MIS-C, 45% were male and 58% were African American. The median age was 8 (1–13) years. Ten patients had severe vitamin D deficiency with a mean level of 7.2 ng/ml. Ninety percent of patients with severe vitamin D deficiency had severe disease ($P < 0.001$). Patients with severe vitamin D deficiency had an increased risk of cardiac involvement ($P < 0.001$).
Conclusions: We describe a potential association between severe vitamin D deficiency and severe disease in children presenting with MIS-C. Severe vitamin D deficiency predisposes patients for cardiovascular involvement and may play a critical role in the host immune response to COVID-19 infection. Future prospective studies at the basic science and clinical level should be pursued to better delineate this association.

1. Introduction

The outbreak of the novel coronavirus disease (Covid-19) has caused a dramatic impact worldwide with more than 160 million cases diagnosed and more than 3 million deaths since the onset of this global pandemic [1]. Initial reports described the pediatric population as low risk for severe Covid-19 disease [2,3]. However, in the last several months, a life-threatening presentation in the pediatric population, known as multisystem inflammatory syndrome in children (MIS-C), has emerged related to a late presentation of Covid-19 infection [4–8]. The clinical presentation of MIS-C has varied in severity; some patients have mild disease, some require critical care, and unfortunately, some have died [9–12]. Recently, adult studies have postulated a link between severity of Covid-19 infection and severe vitamin D deficiency, based on observational studies in the Northern Hemisphere. These countries seemed to share lower levels of vitamin D due to reduced sunlight exposure [13–15]. Previous reports have been published regarding the properties of vitamin D and their implications in the acute viral respiratory syndrome caused by Covid-19 [16–18]. Our standalone tertiary care Children's Hospital is located in the heart of downtown Detroit,

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which has seen one of the severe initial outbreaks of Covid-19 in the United States. As a result, we were part of the group reporting one of the first pediatric case series of MIS-C [12]. The objective of the study was to investigate if severe vitamin D deficiency was associated with increased disease severity and cardiac involvement in children with MIS-C.

2. Methods

This is a single center retrospective study including patients ≤ 18 years of age who met criteria for MIS-C upon admission to our hospital. We defined MIS-C by the Centers for Disease Control and Prevention (CDC) definition: Patients <21 years of age with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem ≥2 organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological) and no alternative plausible diagnoses and positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed Covid-19 case within the 4 weeks prior to the onset of symptoms [19]. We excluded patients who were found to have other infectious etiology for their initial clinical presentation and those with incomplete medical records. The study period corresponded from March to July 2020. The main variable was severe vitamin D deficiency, and the primary outcome was the composite variable severe disease, which was defined as positive if the patients required inotropic support, mechanical ventilation, or venoarterial extracorporeal membrane oxygenation (VA ECMO), or if the disease resulted in death. The secondary outcome was cardiac involvement, consisting of abnormal electrocardiogram, ventricular dysfunction, coronary abnormalities, or pericardial effusion on echocardiogram. Ventricular dysfunction was defined as a shortening fraction less than 28% or ejection fraction less than 50%. The Institutional Review Board at Wayne State University and the Detroit Medical Center research institute approved this study. This was a retrospective chart review, the Institutional Review Boards at Wayne State University waived parental informed consent.

2.1. Data collection

Demographic and clinical data included age, gender, race, weight, height, and comorbidities. Laboratory measurements collected included 25-OH vitamin D level, serum calcium level, serum phosphorus level, nasal swab PCR for SARS-CoV-2 (Covid-19 PCR), immunoglobulin G antibody assay for SARS-CoV-2 (Covid-19 IgG), troponin levels, brain natriuretic peptide (BNP), and creatinine. As part of the initial assessment of all suspected MIS-C cases, a thorough laboratory evaluation, which included 25-OH vitamin D levels, was routinely obtained in order to define this new infectious entity. Initial echocardiography and electrocardiography data were collected. The method to quantify ejection fraction was the area-length or bullet method using the formula V = 5 / 6 × short-axis basal area × LV length, where the short-axis basal area was measured from parasternal short-axis views, and LV length was measured from apical 4-chamber view. The other method used was the M-mode measurement of shortening fraction (SF); this calculated the percentage change in LV volume from end diastole to end systole using parasternal short-axis view of the left ventricle [20]. Severe vitamin D deficiency was defined as Vit D < 10 ng/ml and normal vitamin D levels are considered to be >20 ng/ml [21]. Length of stay in the hospital and the pediatric intensive care unit (PICU) were also obtained. In addition, we calculated the vasoactive-inotropic score (VIS), widely used scoring system for cardiovascular support in pediatric patients that predicts morbidity and mortality in PICU [22,23].

2.2. Statistical analysis

Statistical analysis was performed using SPSS 25 software for PC (IBM Inc.). Demographic continuous variables were expressed as median with interquartile range (IQR) and the categorical variables were expressed in absolute counts with percentage. The entire cohort was divided into two groups based on our main variable vitamin D deficiency. The Student *t*-test and the Chi square test were used as appropriate for statistical comparisons between the groups with and without severe vitamin D deficiency. Logistic regression analysis was used to evaluate the association between vitamin D and all other statistically significant variables in relationship to our primary outcome. Secondary analysis was performed to evaluate the association of cardiac involvement to severe vitamin D deficiency. Statistical significance was taken as a P value of <0.05.

3. Results

The study cohort included 31 patients, with median (IQR) age of 8 (1–13) years, median weight of 32.3 (16–67.7) kg, median height of 130 (93–158) cm, and 14 (45.2%) were males. The cohort included 18 African American patients (58.1%), 4 Caucasian patients (12.9%), and 9 patients of other races (29%). There were 12 (38.7%) patients who had one or more comorbidities. The most common comorbidities were asthma (n = 6), obesity (n = 6), and type 1 diabetes (n = 2). Other comorbidities included systemic hypertension, obstructive sleep apnea, seizure disorder, and propionic acidemia. The baseline demographic and clinic characteristics of the entire cohort are depicted in Table 1.

3.1. Severe vitamin D deficiency and disease severity

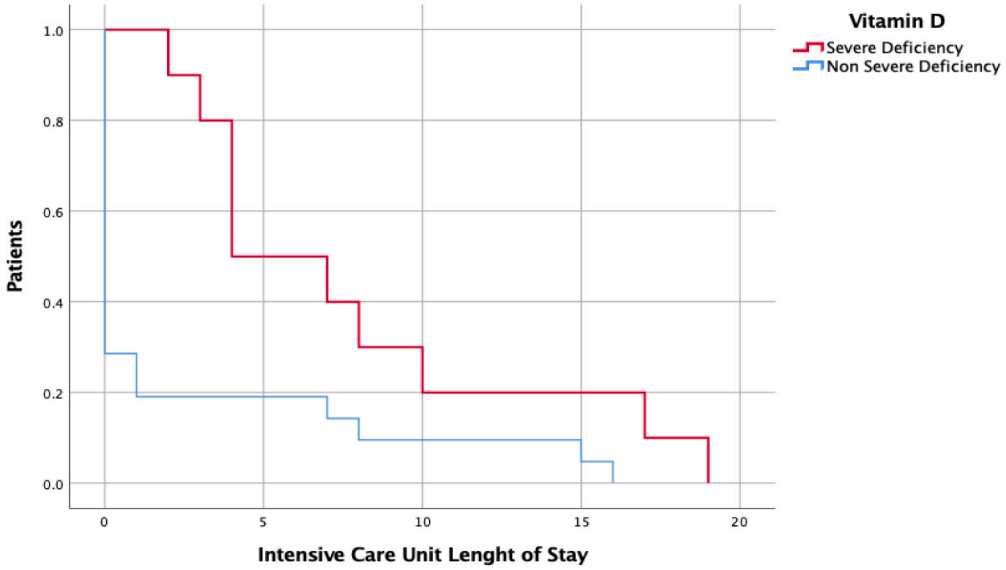
There were 10 (32.3%) patients with severe vitamin D deficiency with a mean (±standard deviation) 25-OH vitamin D level of 7.2 (±0.42) ng/ml. This group had lower levels of serum calcium (8.3 mg/dl vs. 9.2 mg/dl, P < 0.001), and phosphorus (3.4 mg/dl vs. 4.3 mg/dl, P = 0.051) compared with the rest of the cohort. The rest of the cohort had a mean 25-OH vitamin D level of 22.8 (±9.9) ng/ml. Patients with severe vitamin D deficiency had longer ICU (P = 0.02) and hospital length of stay (P = 0.05) than the rest of the cohort (Kaplan-Meier analysis, Figs. 1 and 2). Patients with severe vitamin D deficiency were more likely to have severe disease (P = 0.001). In the group with severe vitamin D deficiency, 9 (90%) patients were positive for our composite outcome of severe disease. All patients with severe vitamin D deficiency and severe disease were positive for Covid-19 IgG.

In the group of patients with severe disease (n = 14); 14 (100%) patients required inotropic support, 6 (42.8%) patients needed invasive mechanical ventilation, and 2 (14%) patients required VA ECMO support. There were no deaths during the study period. Table 2 compares other variables between the group with severe disease to the rest of the cohort.

Table 1
Baseline demographic characteristics.

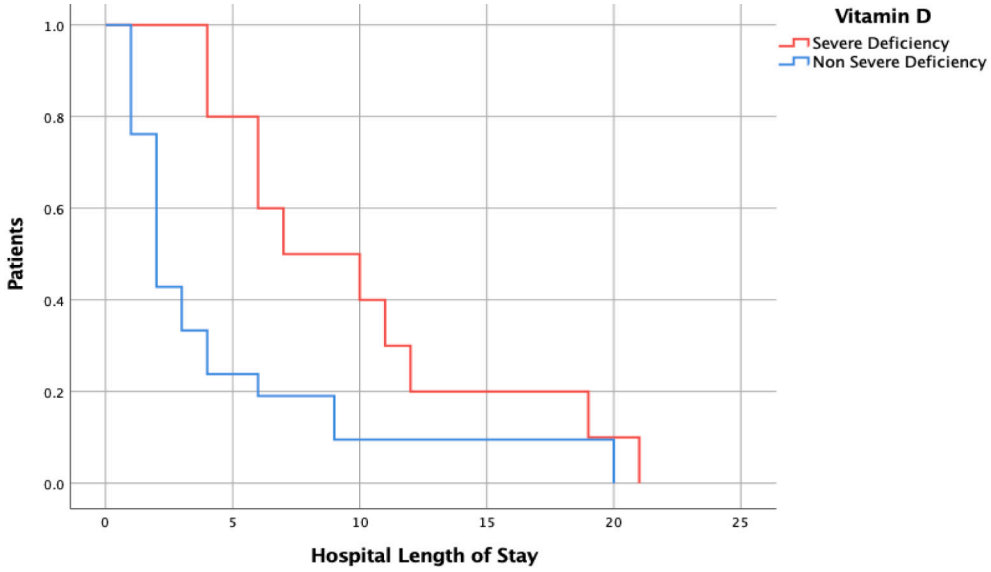
Characteristics (median (IQR) OR n %)	Patients (N = 31)
Age, years	8 (1–13)
Weight, kg	32.3 (16–67.7)
Height, cm	130 (93–158)
Male	14 (45.1%)
Caucasian	4 (12.9%)
African American	18 (58.1%)
Other races	9 (29%)
Severe vitamin D deficiency (≤10 ng/ml)	10 (32.2%)
Covid-19 PCR positive	10 (32.2%)
Covid-19 IgG positive	15 (67.7%)
Need for inotrope support	14 (4.5%)
Need for mechanical ventilation	6 (19.3%)
Need for VA ECMO	2 (6.5%)
Mortality	0 (0%)

Data is presented as n (%) for categorical variables and mean (25th–75th percentiles) for continuous variables. Covid-19: novel coronavirus disease; VA ECMO: venoarterial extracorporeal membrane oxygenation.



Log rank: p: 0.011
ICU: Intensive Care Unit

Fig. 1. ICU length of stay
Log rank: P: 0.011.
ICU: intensive care unit.



Log Rank: 0.025

Fig. 2. Hospital length of stay
Log Rank: 0.025.

The group with severe vitamin D deficiency had an increased risk of severe disease by MIS-C (OR: 28.8; 95% CI; 2.9–286.4; P < 0.01). Table 3 compares several other variables like comorbidities, peak troponin, peak BNP, peak creatinine, and peak GFR between the groups with severe vitamin D deficiency and the rest of the cohort. In the group with severe vitamin D deficiency, the mean peak VIS score during the first 72 h was 6.6 (±6.5) with a mean duration of inotropes of 67.5 (±56.3) hours. There was no independent association by multivariate logistic regression analysis between severe vitamin D deficiency and any of the variables relevant by univariate analysis in a model that included age, ethnicity, comorbidities, peak BNP, peak creatinine, peak GFR, VIS score, ICU and hospital length of stay. Similarly, there was no independent association between severe disease and any of the variables relevant by univariate analysis in a model that included age, comorbidities, PICU length of stay, hospital length of stay, mechanical ventilation, inotropic support, and VA ECMO requirement.

Table 2
Severe disease.

Clinical characteristic Mean (SD) or n (%)	Severe disease (n = 14)	No severe disease (n = 17)	P value
Age, years	10.4 (4.4)	6.1 (5.6)	0.03
Comorbidities	9 (64.3%)	3 (17.6%)	<0.01
PICU length of stay, days	8.79 (5.7)	0.18 (0.5)	<0.01
Hospital length of stay, days	11.4 (6)	2.2 (1)	<0.01
Mechanical ventilation	6 (42.8%)	0 (0%)	<0.01
Inotropic support	14 (100%)	0 (0%)	<0.01
VA ECMO	2 (14%)	0 (0%)	<0.01

SD: standard deviation, Covid-19: novel coronavirus disease; ICU: pediatric intensive care unit; VA ECMO: veno-arterial extracorporeal membrane oxygenation.

Table 3
Severe vitamin D deficiency.

Clinical characteristic Mean (SD) or n (%)	Severe vit D deficiency (n = 10)	Normal vit D (n = 21)	P value
Age, years	11.3 (3.3)	7.2 (5.8)	0.052
Weight, kg	55.6 (30.6)	38.2 (36)	0.199
Height, cm	148 (19)	117 (36)	0.02
Male gender	4 (40%)	10 (47%)	0.69
African American race	8 (80%)	10 (47%)	0.17
Comorbidities	5 (50%)	7 (33%)	0.37
Severe disease	9 (90%)	5 (24%)	0.001
Covid-19 PCR, positive	4 (40%)	6 (29%)	0.5
Covid-19 IgG, positive	9 (90%)	6 (28%)	0.005
Ca, mg/dL	8.3 (0.5)	9.2 (0.5)	0.001
Peak troponin, ng/L	968 (1765)	303 (755)	0.148
Peak BNP, pg/mL	2152 (1758)	516 (926)	0.003
Peak creatinine, mg/dL	1.4 (1.2)	0.7 (0.6)	0.034
Peak GFR, ml/min	63 (30)	94 (44)	0.05
PICU length of stay, days	7.8 (5.9)	2.2 (4.9)	0.02
Hospital length of stay, days	10 (5.9)	4.6 (5.6)	0.05
VIS score	6.6 (6.5)	1.9 (4.8)	0.03
Left ventricular ejection fraction, %	44.9 (15.5)	64 (9.4)	<0.001
Left ventricular shortening fraction, %	22.8 (9.2)	34.5 (6.3)	<0.001

SD: standard deviation, Covid-19: novel coronavirus disease; BNP: brain natriuretic peptide; GFR: glomerular filtration rate; PICU: pediatric intensive care unit; VIS: vasoactive-inotropic score.

3.2. Cardiac involvement

There were 13 (41.9%) patients who had cardiac involvement. It consisted of 12 patients with ventricular dysfunction, 4 patients with coronary artery involvement, 5 patients had pericardial effusion and 9 patients had an abnormal electrocardiogram. The group with cardiac involvement had a mean (SD) 25-OH vitamin D level of 9.6 (4.3) ng/ml vs. 23.7 (10.6) ng/ml for the rest of the cohort ($P < 0.01$). The group with severe vitamin D deficiency had an increased risk of cardiac involvement (OR: 38.3; 95% CI; 3.7–395.3; $P < 0.01$). Additionally, those with severe vitamin D deficiency had reduced left ventricular ejection and shortening fraction compared to the group with non-severe vitamin D deficiency ($P < 0.001$). There was no association by multivariate logistic regression analysis between cardiac involvement and any of the variables included in the model (age, ethnicity, comorbidities, severe vitamin D deficiency, peak BNP, peak creatinine, peak GFR, VIS score, ICU and hospital length of stay).

4. Discussion

We report an association between severe vitamin D deficiency and severe disease in children with MIS-C. In addition, severe vitamin D deficiency was associated with cardiac involvement, prolonged ICU, and hospital length of stay. To our knowledge, this is the first study to report an association between vitamin D deficiency and illness severity in pediatric patients with MIS-C. Although no variable remained associated by multivariate analysis, we postulate that the reason for this was the small sample size and that several variables were individually associated with severe disease, hence, making regression analysis difficult to interpret in a small sample cohort.

4.1. Severe vitamin D deficiency and severe disease

Previous studies in adults have described an association between low vitamin D levels and Covid-19 infection [24,25]. Merzon et al. included 7807 individuals who had vitamin D levels and were tested for Covid-19. They reported that low vitamin D; defined in their study as <30 ng/mL; was a risk factor for infection and hospitalization, independent of demographic characteristics and previous medical conditions [24]. D'Avolio et al. reported the association between lower vitamin D levels and positive PCR test for Covid-19. Their cohort included 107 patients, of which 27 patients were positive for Covid-19 PCR. Vitamin D levels were lower in the group with Covid-19 infection, median of 11.1 ng/ml vs. 24.6 ng/ml ($P = 0.004$) [25]. In a different manner, our cohort included only pediatric patients with evidence of Covid-19 infection and reported that severe vitamin D deficiency was associated with increased morbidity.

Previous studies in critically ill children have shown an association between severe disease and vitamin D deficiency [26,27]. Moreover, a recent study reported that a single dose of vitamin D given to pediatric patients with vitamin D deficiency could reduce the incidence of septic shock in specific patient populations [28]. Furthermore, a meta-analysis in 2017 reported that vitamin D deficiency in patients admitted to the pediatric ICU could lead to increased mortality, higher incidence of multi organ dysfunction, and overall worse clinical course for the respective illness [29]. Similarly, we describe association between severe MIS-C and severe vitamin D deficiency in our cohort. Although vitamin D deficiency is a common occurrence in our community, it is notable that almost all children with severe MIS-C had concurrent severe vitamin D deficiency. The etiology of this association can be related to the known immune modulatory role of vitamin D, since the current accepted pathophysiology of MIS-C is related to an altered and exaggerated immune response [30].

4.2. Cardiac involvement

The role of vitamin D in cardiovascular pathophysiology has been studied extensively, with vitamin D deficiency being a common finding in patients with cardiovascular disease [31]. It has been postulated that vitamin D plays an essential role in endothelial function, mediated by vitamin D receptors (VDRs). These VDRs are expressed in many cells and tissues of the cardiovascular system, including vascular smooth muscles, endothelium, and myocardium [32]. Furthermore, vitamin D regulates numerous genes involved in the pathogenesis of cardiovascular disease, controlling cell proliferation and differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, and cell adhesion. Endothelial stress leads to proliferation and migration of vascular smooth muscle cells which is inhibited by $25(OH)D_3$ and $1,25(OH)_2D_3$ [33].

Lipshultz et al. described how low PTH level and subsequently lower intracellular calcium concentrations in patients with chronic renal disease correlated strongly with ischemia, depressed contractibility, and adverse outcomes [34]. Similarly, Margosian et al. described that vitamin D deficiency and elevated PTH levels were associated with lower LV mass z-scores while FGF-23 was inversely related to end-diastolic septal thickness [35]. Similarly, we described that patients with MIS-C and severe vitamin D deficiency had reduced left ventricular ejection and shortening fraction compared to their counterparts with MIS-C and normal vitamin D levels, although our cohort was small.

Additionally, McNally et al. reported vitamin D levels in patients following pediatric cardiac surgery. They demonstrated that vitamin D deficiency was associated with prolonged mechanical ventilation and ICU stay after pediatric cardiac surgery [31]. Similarly, Dohain et al. found that postoperative vitamin D level was inversely associated with postoperative inotropic requirement in pediatric patients following cardiac surgery [36]. We postulate that patients with severe vitamin D deficiency have non-ideal baseline endothelial function, oxidative stress, membrane transport, and cell matrix homeostasis. These factors would put them at higher risk for significant cardiovascular involvement and predispose them to myocardial malfunction, endothelial dysfunction, peripheral edema, shock, pulmonary edema, and hypotension, which are all key clinical manifestations of severe cardiac involvement and illness due to MIS-C.

4.3. Limitations

The study is a single center retrospective study with a relatively small number of patients. In addition, data collection and statistical analysis were limited to data already recorded in the medical records. Despite our retrospective design, one of the strengths of our study compared with similar reports in adults is that vitamin D levels were obtained in patients meeting criteria for MIS-C within 2 days of hospital admission. Unfortunately, we were not able to obtain additional laboratory (parathyroid hormone level) or imaging data (wrist X ray) that would further support the diagnosis of vitamin D deficiency as these tests were not routinely obtained during their hospitalization due to the critical nature of their illness. However, the patients in our severe vitamin D deficiency group did have overall lower levels of calcium and phosphorous compared to the rest of the cohort, which suggests that these patients likely had severe vitamin D deficiency.

5. Conclusion

We describe a potential association between severe vitamin D deficiency and severe disease in children presenting with MIS-C due to Covid-19. Severe vitamin D deficiency predisposes patients for cardiovascular involvement due to altered cellular homeostasis mediated by widespread VDRs in the cardiovascular system. Furthermore, the immune modulatory activity of vitamin D may play a critical role in the host immune response to Covid-19 infection. Future prospective studies at the basic science and clinical level should be pursued to better delineate this association.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human medical regulations and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the ethical committee of Children's Hospital of Michigan.

Disclosure

This was a retrospective chart review by the IRB (Institutional Review Boards) at Wayne University waived parental informed consent.

CRediT authorship contribution statement

Diana Torpoco Rivera: conceptualization, methodology, formal analysis, writing - original draft. **Amrit Misra:** resources, formal analysis, writing - review & editing. **Yamuna Sanil:** supervision, writing - review & editing. **Natalie Sabzghabaei:** supervision, writing - review & editing. **Raya Safa:** supervision, writing - review & editing. **Richard Garcia:** formal analysis, supervision, writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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