Is Vitamin D Deficiency a Risk Factor for Covid 19 in Children ?

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Abstract

Objective: In this study, we aimed to determine the prevalence and clinical importance of vitamin D deficiency in children and adolescent patients who were hospitalized with the diagnosis of COVID-19. Material and Methods: 40 patients who were diagnosed to have COVID-19 and hospitalized with the real-time reverse transcription polymerase chain reaction (RT-PCR) method were included. The control group consisted of 45 healthy patients with normal vitamin D levels. The age of admission, clinical and laboratory data, and 25-hydroxycholecalciferol (25-OHD) and parathormone (PTH) levels were recorded. Those with vitamin D levels which are below 20 ng/ml were determined as Group 1 and those with [?]20 ng/ml as Group 2. Results: The median levels of vitamin D level were 13.14 (4.19-69.28) in the group of patients with COVID-19 and 34.81(3.8-77.42) in the control group. Compared to the control group, there was a statistically significantly lower vitamin D level ($p < 0.001$) in the COVID-19 patient group. At admission, the symptom of fever was significantly higher in Group 1 than in Group 2 ($p = 0.038$). The distribution of disease severity according to vitamin D levels was not found significantly different. In conclusion; our study is the first to evaluate vitamin D levels and its relationship with clinical findings in pediatric patients diagnosed with COVID-19. There are significantly lower levels of vitamin D in children with COVID-19 than those in the control group. This shows that vitamin D, which is effective in the immunological mechanism, also has an effect in the physiopathology of the disease.

Introduction

A new coronovirus (CoV) infection was reported to begin in late 2019 in Wuhan, Hubei, China, which the World Health Organization (WHO) called COVID-19 on February 11, 2020 (1). On March 11, 2020, COVID-19 infection was declared a pandemic by WHO due to the global logarithmic increase of cases (2). Studies have reported that crude mortality rates worldwide due to the COVID-19 outbreak vary between 5.6% and 15.2%. The risk of death was found to be higher for elderly individuals and those with comorbid conditions such as hypertension and diabetes mellitus. In an article reviewing 46,248 cases, hypertension, diabetes mellitus, cardiovascular disease and respiratory morbidity were specified to be the most common comorbidities (3).

Vitamin D deficiency is an important problem of global public health which all age groups face. More than one billion people all over the world are estimated to have vitamin D deficiency. Vitamin D is a pluripotent hormone modulating the adaptive and innate immune response(4). The risk of infection by several mechanisms can be reduced by vitamin D. Vitamin D induces cathelicidins and defensins that can lower viral replication rate. It also increases the concentration of anti-inflammatory cytokines, as well as the concentration of pro-inflammatory cytokines that cause pneumonia and lung damage (1). In previous studies, vitamin D deficiency has been shown to increase respiratory infections risk including respiratory syncytial virus (RSV), tuberculosis and flu, and is a risk factor for acute respiratory distress syndrome (ARDS) (4).

The SARS-CoV-2 virus among the COVID-19 patients, enters host cells by binding to receptors of angiotensin-converting enzyme 2 (ACE2) in the respiratory tract of infected patients (5). The primary

targets of coronaviruses are type-II pneumocytes and there is high expression of ACE2 receptors in these cells. The level of surfactant can be reduced due to dysfunction of Type-II pneumocytes, increasing surface tension in COVID-19 (6). It has been shown that surfactant synthesis in alveolar type-II cells is stimulated by 1,25-dihydroxyvitamin D metabolites (7). To protect the lung against acute injury and prevent the vitamin D deficiency which is regarded as a COVID-19 pathogenic factor, Vitamin D agonist calcitriol modulates expression of the renin -angiotensin system members such as ACE2 in tissue of lung (8). Vitamin D is a secosteroid with a wide range of immunomodulatory, anti-inflammatory, of antifibriotic and antioxidant effects. Inflammatory cytokine expression [eg, IL-la, IL-la, tumor necrosis factor-α] ις ινηιβιτεδ βψ ιταμιν Δ ανδ τηερε ις ασσοχιατιον βετωεεν ιτς δεφιχιενχψ ανδ οερ-εξπρεσσιον οφ Τηλ χψτοκινες (9). Επιδεμιολογιχαλ στυδιες ηαε ρεπορτεδ αν ασσοχιατιον βετωεεν ιταμιν Δ δεφιχιενχψ ανδ αχυτε λυνγ ινθυρψ ανδ ιραλ ρεσπιρατορψ ινφεχτιονς (10). ὃνσεχυεντλψ, τηε ιμμυνε ρεσπονσε αγαινστ ρεσπιρατορψ ιρυς ινφεχτιονς σηουλδ βε ιμπροεδ βψ α συφφιχιεντ λεελ οφ 25 (OH) Δ ιν σερυμ (11). 1,25-διηψδροξψ ιταμιν Δ3 ινχρεασες τηε αβσορπτιον οφ ἃ φρομ δυοδενυμ ανδ πηοσπηορυς φρομ ιλευμ. Ιτ αλσο πρεεντς τηε λοσς οφ χαλχιυμ ιν τηε κιδνεψς ανδ ινχρεασες βονε ρεσορπτιον.

Ιν τηις στυδψ, ωε αιμεδ το δετερμινε τηε πρεαλενχε ανδ χλινιχαλ ιμπορτανχε οφ ιταμιν Δ δεφιχιενχψ ιν χηιλδρεν ανδ αδολεσχεντ πατιεντς ωηο ωερε ηοσπιταλιζεδ ωιτη τηε διαγνοσις οφ ΫΟΫΙΔ-19.

Ματεριαλ ανδ Μετηοδς

85 πατιεντς αγεδ 1 μοντη το 18 ψεαρς ωηο αππλιεδ το Δισλε Υνιερσιτψ Φαχυλτψ οφ Μεδιχινε βετωεεν 15.03.2020 ανδ 20.05.2020 ωερε ινχλυδεδ ιν τηε στυδψ. 40 πατιεντς ωηο ωερε διαγνοσεδ το ηαε ΫΟΫΙΔ-19 ανδ ηοσπιταλιζεδ ωιτη τηε ρεαλ-τιμε ρεερσε τρανσχριπτιον πολψμερασε χηαιν ρεαχτιον (ΡΤ-ΠΫΡ) μετηοδ ωερε ινχλυδεδ. Τηε χοντρολ γρουπ ωας χομποσεδ οφ 45 ηεαλτηψ πατιεντς ωηο ηαδ πρειουσλψ αππλιεδ το Πεδιατριχ Ενδοχρινολογψ ορ Πεδιατριχ ουτπατιεντ χλινιχς ανδ ωηοσε ιταμιν Δ λεελ ωας χηεχκεδ. Τηοσε ωιτη χηρονις δισεασες ανδ αν αδδιτιοναλ δισεασε, ανδ τηοσε ψουνγερ τηαν 1 μοντη ανδ ολδερ τηαν 18 ωερε εξχλυδεδ φρομ τηε στυδψ. Τηε δατα οφ τηε χασες ινχλυδεδ ιν τηε στυδψ ωερε οβταινεδ φρομ ρετροσπεχτιε φιλε ρεχορδς. Τηε αγε οφ αδμισσιον, χλινιχαλ ανδ λαβορατορψ δατα, ανδ 25-ηψδροξψχηολεχαλχιφερολ (25-ΟΗΔ) ανδ παρατηορμονε (ΠΤΗ) λεελς ωερε ρεχορδεδ. 25-ηψδροξψχηολεχαλχιφεραολ λεελ ωας εξαμινεδ ιν Σημματζυ δειχε βψ ηιγη περφορμανχε λιχυιδ χηροματογραπηψ μετηοδ. ΠΤΗ λεελ ωας εξαμινεδ βψ ελεχτρο χηεμιλυμινεσχενχε μετηοδ ιν Σιεμενς Αδια ἓνταυρ δειχε. Τηοσε ωιτη 25-ΟΗΔ λεελ <12νγ/μλ ωερε χονσιδερεδ ας ιταμιν Δ Δεφιχιενχψ, τηοσε βετωεεν 12-20 νγ/μλ ωερε χονσιδερεδ ας Ινσυφφιχιενχψ οφ ιταμιν Δ ανδ τηοσε ωιτη >20 νγ/μλ ωερε χονσιδερεδ Συφφιχιενχψ (12). Πατιεντς διαγνοσεδ ωιτη ΫΟΫΙΔ-19 ωερε διιδεδ ιντο 2 γρουπς. Τηοσε ωιτη ιταμιν Δ λεελς ωηιχη αρε βελοω 20 νγ/μλ ωερε δετερμινεδ ας Γρουπ 1 ανδ τηοσε ωιτη [;]20 νγ/μλ ας Γρουπ 2, ανδ χλινιχαλ ανδ λαβορατορψ αριαβλες βετωεεν τηε 2 γρουπς ωερε χομπαρεδ.

Τηε στυδψ ωας χονδυχτεδ βασεδ ον τηε ρυλες οφ Δεχλαρατιον οφ Ηελσινκι ανδ αππροεδ βψ τηε Ινστιτυτιοναλ Ετηιχς ὃμμιττεε οφ Δισλε Υνιερσιτψ, Φαχυλτψ οφ Μεδιχινε.

Στατιστιχαλ Αναλψσις

Δατα αναλψσες ωερε εξαμινεδ βψ υσινγ Στατιστιχαλ Παχκαγε φορ Σοχιαλ Σχιενχες (ΣΠΣΣ), ἔρσιον 20.0 φορ Ωινδοως (ΣΠΣΣ Ινχ., ἤιχαγο, ΙΛ, ΥΣΑ). Τηε αριαβλες ωερε ινεστιγατεδ υσινγ ισυαλ (ηιστογραμς, προβαβιλιτψ πλοτς) ανδ αναλψτιχαλ μετηοδς (Κολμογορο-Σιμιρνο τεστ) ωηετηερ ορ νοτ τηεψ ωερε νορμαλλψ διστριβυτεδ. Νορμαλλψ διστριβυτεδ αριαβλες ωερε πρεσεντεδ υσινγ μεανς ανδ στανδαρδ δειατιονς, ανδ νον-νορμαλψ διστριβυτεδ αριαβλες υσινγ μεδιαν ανδ ρανγε (μαξιμυμ ανδ μινιμυμ). ὃμπαρισιονς οφ τηε γρουπς ωερε περφορμεδ υσινγ τηε Στυδεντ τ (νορμαλλψ διστριβυτεδ αριαβλες) ανδ Μαννν-Ωηιτνεψ Υ (νον νορμαλλψ διστριβυτεδ αριαβλες). Τηε χηι-σχυαρε τεστ ωας υσεδ το αναλψζε οφ χατεγοριχαλ αριαβλες. Π αλυες <0.05 ωερε χονσιδερεδ στατιστιχαλλψ σιγνιφιχαντ.

Ρεσυλτς

ΫΟΫΙΔ-19 Πατιεντσ΄ μεαν αγε ωας 101.76 ± 27.91 (3 months-18 years) and 75.68 ± 27.34 (1 month-18 years) in the healthy control group. 47.5% (n=19) of the patients and 60% (n=27) of the control group were male. No difference was found between the groups in terms of age and gender distribution (p = 0.061, p=0.248,

respectively). The median levels of vitamin D level were 13.14 (4.19-69.28) in the group of patients with COVID-19 and 34.81 (3.8-77.42) in the control group. When the COVID-19 patient group and the healthy control group were compared, there were statistically significantly lower serum phosphorus level ($p<0.001$) and vitamin D level ($p<0.001$) in the COVID diagnosed patient group. Table 1 depicts the comparison of demographic and laboratory characteristics between COVID 19 patient group and healty control subject group.

Patients diagnosed with COVID-19 were divided into 2 groups. Those who had deficient and insufficient vitamin D levels were determined as Group 1 (n: 29, 72.5%) and normal patients were determined as Group 2 (n: 11, 27.5%). 18 patients in Group 1 were deficient in vitamin D and 11 were insufficient. When the clinical and laboratory parameters of Group 1 and Group 2 are compared, at admission, the symptom of fever (34.5%) was significantly higher in Group 1 than in Group 2 (0%) ($p = 0.038$). There were significantly lower levels of vitamin D ($p<0.001$) and serum phosphorus ($p=0.013$) in group 1 than those in group 2. No significant difference was found between other clinical and laboratory parameters between the groups. Comparison of demographic, clinical and laboratory characteristics between COVID 19 diagnosed childrens who had deficient and insufficient level of vitamin D (group 1) and covid 19 diagnosed childrens who had normal level of vitamin (group 2) is shown in Table 2.

The distribution of disease severity according to vitamin D levels was not found significantly different (Table 3).

There was a negative correlation found between fever symptom and vitamin D level ($p = 0.023$, Table 4).

Discussion

Our study evaluated the vitamin D deficiency prevalence and the association between vitamin D deficiency and clinical and inflammatory markers in our patients hospitalized for COVID-19 infection. To the best of our knowledge, we have not found any study on vitamin D levels in pediatric patients diagnosed with COVID-19 in our literature review of resources in English. We aim to investigate whether children diagnosed with COVID-19 had vitamin D deficiency as well as the realationship between vitamin D deficiency and clinical outcomes.

Although there are no adequate studies on vitamin D levels and its effects in children with COVID-19, there are several studies evaluated the relationship between other respiratory pathogens and vitamin D. In some clinical studies, vitamin D has been shown to protect children from lung infection. Children with vitamin D deficiency or insufficiency are more susceptible to respiratory infection (13). A meta-analysis and systematic review of 25 randomized controlled trials by Martineau et al. showed that vitamin D generally protects against acute respiratory infection (14). In an important study covering 1582 people by Li et al. with aim of determining the relationship between 25(OH)D in children and pulmonary infection, the community-acquired pneumonia group displayed a lower value than the control group, and there were also significant differences between the pneumonia group and pneumonia-derived sepsis group (p <0.001), and there was association between lower serum 25(OH)D level and more serious symptoms (15).

Daneshkhah et al. observed that high CRP was inversely correlated with 25(OH)D, and they thought vitamin D to have a possible role in reduction of complications caused by abnormal inflammation and cytokine storm given the CRP as a marker for cytokine storm and considering its association with vitamin D deficiency (16). Some previous studies found negative correlation between 25(OH) D vitamin level and pneumonia severity, CRP level, increased risk of sepsis, ARDS risk and increased production of proinflammatory cytokines such as IL-6 (17-21). In the present study, a negative correlation was found between vitamin D level and fever symptom ($p = 0.023$), but there was no significant finding in terms of CRP level and clinical severity.

In a study conducted by Alipio M et al. observed that vitamin D level was low or insufficient in 74.1% of patients diagnosed with COVID 19 and also found a statistically significant difference between serum 25(OH)D level and clinical outcomes ($p <0.001$) (22). In another study of Lau et al. regarding the relationship between vitamin D deficiency and the severity of COVID-19 disease in adult age group, low levels of vitamin

D were found in 75% of the cases and 84.6% of the patients in intensive care unit (23). In a study conducted on adults, Raharusa et al. found deficient or insufficient levels of vitamin D in 47.3% of 780 patients diagnosed with COVID-19. Vitamin D was insufficient in 27.3% of them and deficient in 20% of them. They observed mortality in 49.1% of vitamin D insufficient cases, 46.7% of deficient ones and 4.1% of normal ones, and found statistically significant results between vitamin D level and mortality ($p < 0.001$). However, the comorbid factors concomitant with the majority of those with deficient and insufficient vitamin D levels in their studies make it difficult to evaluate the relationship between mortality and vitamin D alone (24). In our study, 72.5% of our cases were vitamin D deficient or insufficient, and 2 patients (100%) in need of treatment in the intensive care unit had the vitamin D level of below 10 ng/ml, and had comorbid diseases, but none of them had mortality. In our study, the distribution of disease severity according to vitamin D levels was not found significantly different ($p = 0.097$). Yet, although the virulence mechanisms related to COVID-19 are not fully characterized, the fact that clinical severity and mortality rate of the disease generally progress better in children compared to adults suggests that it may be due to Ace 2 receptor count and cytokine storm being less than that of adults depending on immunological response. When COVID 19 diagnosed childrens who had deficient and insufficient level of vitamin D (group 1) and covid 19 diagnosed childrens who had normal level of vitamin (group 2) compared at admission, Group 1 had significantly higher fever symptom (34.5%, 10) than Group 2 (0%) ($p = 0.038$). A negative correlation was found between vitamin D level and fever symptom ($p = 0.023$), but there was no significant finding in terms of CRP level and clinical severity.

A study conducted by Ilie et al., found that average vitamin D levels in each country and the COVID-19 cases were negatively correlated with the number of deaths caused by COVID-19 (25). Since there were no patients in our study who died, there was no evaluation of the relationship between vitamin D levels and mortality.

In conclusion, our study is the first to evaluate vitamin D levels and its relationship with clinical findings in pediatric patients diagnosed with COVID-19. There are significantly lower levels of vitamin D in children with COVID-19 than those in the control group. This shows that vitamin D, which is effective in the immunological mechanism, also has an effect in the physiopathology of the disease. Vitamin D levels are associated with fever. Since we did not have any patients lost, their relationship with mortality could not be evaluated. More studies are needed in children for evaluation of the association between vitamin D with clinical and laboratory findings of the disease and its effect on mortality.

Conflict of Interest

None

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KY and VS wrote the manuscript. All authors read and approved the final manuscript.

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