Section: Paediatrics

Original Research Article

TO INVESTIGATE THE CORRELATION BETWEEN SERUM VITAMIN D LEVELS AND THE OUTCOME OF CRITICALLY ILL CHILDREN

Rajkumar[1], Ruchin Agarwal[1]

[1]Assistant Professor, Department of Paediatrics, Rajshree Medical Research Institute Bareilly, Uttar Pradesh, India.

Received : 05/11/2022
Received in revised form : 25/12/2022
Accepted : 10/01/2023

Keywords:
Vitamin D, Critically ill, Children, VDD, PICU.

Corresponding Author:
Dr. Ruchin Agarwal,

DOI: 10.47009/jamp.2023.5.1.209

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (1); 1007-1012

Abstract

Background: To investigate the correlation between serum vitamin D levels and the outcome of critically ill children. **Materials and Methods:** The research included all patients hospitalised to the PICU who had 25-hydroxyvitamin D (25(OH)D) levels available within 24 hours of admission. Only the first PICU admission of each patient was included in the research. Randomly collected 25(OH)D levels were obtained during the first 24 hours of admission to the PICU. Upon admission to the PICU, essential information about the patient was documented, such as their age, gender, BMI in kilogrammes per square metre (kg/m2), pre-existing medical conditions, cause for admission, time of year, and if they had a history of Vitamin D supplementation. Analysed were laboratory variables acquired during the first 24 hours after hospital admission, including serum levels of total calcium, ionised calcium, phosphate, magnesium, and 25(OH)D. **Results:** Out of the total number of patients, 40 individuals, accounting for 40% of the sample, were under the age of 2 years. Neurologic illnesses accounted for 22% of the causes for admission to the Paediatric Intensive Care Unit (PICU), followed by respiratory tract infections at 21% and sepsis at 15%. The average 25(OH)D level of the entire groups was 20.11 ± 2.47 ng/ml. The VDD (25[OH]D levels below 20 ng/ml) was measured in 70 children, which accounted for 70% of the total. The average 25(OH)vitD levels were comparatively lower (17.11 ± 3.41 ng/ml) in children who had sepsis at admission, as opposed to other critically sick patient groups (21.04 ± 2.88). However, this difference did not reach statistical significance (P = 0.07). During their stay in the PICU, 10 patients, accounting for 10% of the total, unfortunately passed away. **Conclusions:** We concluded that the prevalence of Vitamin D deficiency was significantly high among Indian children upon admission to the PICU. There was no notable link seen between several indicators of sickness severity, such as death, and the amount of Vitamin D.

INTRODUCTION

Vitamin D is a crucial hormone that is necessary for healthy health.[1] Vitamin D is a fat-soluble vitamin that may be acquired by diet (food or supplements) or produced by the skin, with the skin being the main source. Vitamin D plays a crucial role in the process of bone mineralization and calcium metabolism via its endocrine-like functions.[2,3] The non-classical function encompasses the control of cell proliferation and differentiation, the regulation of hormone production, and the modulation of immunological function. These effects occur at the cellular level and are directly influenced by the substrate-dependent 25(OH)D level.[2] 25(OH)D is the primary form of vitamin D that circulates in the body. It has a half-life of 2-3 weeks and its levels provide the most accurate indication of a person's vitamin D status.[4] Vitamin D is a prohormone that exists in its active state as 1,25(OH)2D.[2] The regulation of serum 1,25(OH)2D is closely controlled by parathyroid hormone (PTH), serum calcium, and fibroblast growth factor 23.[5]

The action of 1,25(OH)2D occurs via the vitamin D receptor (VDR), which is present in several kinds of tissues. In addition, the majority of these cells exhibit the presence of the 25(OH)D-1a-hydroxylase (CYP27B1), which is a mitochondrial P450 enzyme. This enzyme is responsible for producing the active hormone calcitriol, which is used by the target cell itself for autocrine purposes. Furthermore, recent research has shown that vitamin D plays a crucial role in combating infections by enhancing the production of AMPs, namely CAMP, and bolstering the body's defenses.[2] Several genes that encode proteins involved in controlling cell growth, specialisation, and programmed cell death are known to be

ISSN (O): 2687-5365; ISSN (P): 2753-6556

influenced, at least partially, by vitamin D.[6] Vitamin D has recently been the subject of attention due to its involvement in non-skeletal disorders, particularly in relation to immunity.[7] Subclinical vitamin D insufficiency is quite widespread in both children and adults[8]. Vitamin D deficiency (VDD) is a common illness that affects more than one billion individuals globally. It is often overlooked and not properly addressed as a nutritional insufficiency.[9] There is data indicating that India has a high prevalence of subclinical vitamin D insufficiency, despite being located in a low latitude region with abundant sunlight. The prevalence of vitamin D insufficiency in children, as reported in various research, ranges from 75% to 90%.[10] In India, community-based research have shown a prevalence of vitamin D insufficiency ranging from 50% to 90%.[11] Contemporary lifestyles have greatly decreased the overall amount of time that youngsters are exposed to sunlight. UV B rays, with a shorter wavelength, have a tendency to disperse sooner or later in the day. As a result, the synthesis of vitamin D in the skin is at its highest between 10 AM and 3 PM. Unfortunately, at this period, most youngsters are either in school or inside.[12] In addition to sunlight, exposure to endocrine disrupting chemicals such as bisphenol A and phthalates, which are commonly used industrial substances present in many commercial items, might potentially change the levels of blood 25(OH)D3.These substances have been discovered to alter the expression of cytochrome P450 and CYP27B1 genes in mice. Hence, the prevalence of vitamin D insufficiency may be influenced by the exposure to ubiquitous pollutants often seen in Western society.[13,14] Surveys of vitamin D levels in severely ill children often provide divergent and conflicting findings.

MATERIALS AND METHODS

This research was a retrospective analysis that included screening all children between the ages of 1 month and 16 years who were admitted to the medical-surgical PICUs and were ≤18 years old. The research recorded a total of 100 hospitalisations to the PICU. The research included all patients hospitalised to the PICU who had 25-hydroxyvitamin D (25(OH)D) levels available within 24 hours of admission. Only the first PICU admission of each patient was included in the research. Randomly collected 25(OH)D levels were obtained during the first 24 hours of admission to the PICU.

Upon admission to the PICU, essential information about the patient was documented, such as their age, gender, BMI in kilogrammes per square metre (kg/m2), pre-existing medical conditions, cause for admission, time of year, and if they had a history of Vitamin D supplementation. Analysed were laboratory variables acquired during the first 24 hours after hospital admission, including serum levels of total calcium, ionised calcium, phosphate, magnesium, and 25(OH)D.

Blood samples were collected following the standard procedure of drawing blood upon admission to the PICU. The tests were conducted using standard procedures often used in the biochemistry laboratory of our university hospital. The concentration of 25-hydroxyvitamin D (25(OH)D) was assessed on a weekly basis. The samples were shielded from sunlight, subjected to centrifugation, and kept in a refrigerated environment until they were processed. The concentration of 25(OH)D was determined using chromatography in conjunction with the tandem mass spectrometry technique and was expressed in units of ng/mL. VDD was established as a threshold of 25(OH)D levels below 20 ng/ml. The range of values is between 5 and 7, inclusive. The research categorised all the paediatric patients into two groups based on their Vitamin D levels: Vitamin D adequate (25[OH]D ≥20 ng/ml) or Vitamin D deficient (25[OH]D <20 ng/ml).

The main objective of this study was to determine the incidence of vitamin D deficiency (VDD) in critically unwell children. The secondary objectives were to evaluate the factors influencing Vitamin D levels and to compare the severity of sickness between individuals with Vitamin D deficiency and sufficiency. The variables included as indicators of disease severity encompassed the paediatric risk of mortality (PRISM III) score, catecholamine demands, mechanical ventilation, PICU length of stay, and mortality. Sepsis is characterised as a widespread inflammatory response throughout the body when there is a suspected or proven infection caused by any organism in the blood or cerebrospinal fluid.

Statistical Analysis

The data gathered in the research were subjected to statistical analysis using SPSS 25.0 software (IBM Corp. in Armonk, NY, USA). The assessment was conducted using three categories: descriptive analysis, single variable analysis, and multivariable analytic approaches. The categorical data were expressed as numerical values (n) and proportions (%).

An assessment was conducted to see whether the data adhered to a normal distribution. In the context of comparing independent groups, the Mann Whitney U-test was used to compare two groups where the numerical variables did not exhibit a normal distribution. For comparisons involving more than two groups, the Kruskal-Wallis nonparametric analysis of variance was utilised. Chi-square statistics were used to compare categorical data between independent groups. The Cox regression model was used to assess censored time-to-event data in the multi-variable analysis. When examining mortality, a logistic regression model was used to dichotomized data. The quantitative evaluation of Vitamin D level was conducted using a multi-variable linear regression model. The research used a 2-way

ISSN (O): 2687-5365; ISSN (P): 2753-6556

hypothesis structure and a Type-1 error threshold of 5% in all statistical analyses.

RESULTS

The fundamental attributes of the group are shown in Table 1. The trial included 100 critically sick children, with a median age of 5.28±1.58 years. Out of the total number of patients, 40 individuals, accounting for 40% of the sample, were under the age of 2 years. Neurologic illnesses accounted for 22% of the causes for admission to the Paediatric Intensive Care Unit (PICU), followed by respiratory tract infections at 21% and sepsis at 15%. Based on the family history, it was found that 80 patients had been receiving Vitamin D supplementation prior to admission, with the majority (80%) being under the age of 2.

The average 25(OH)D level of the entire groups was 20.11 ± 2.47 ng/ml. The VDD (25[OH]D levels below 20 ng/ml) was measured in 70 children, which accounted for 70% of the total. There was a correlation between a past record of Vitamin D administration and elevated levels of 25(OH) vitamin D. Children who had taken Vitamin D supplements had significantly higher mean 25(OH)D levels compared to children who had not taken any Vitamin D supplements (30.17 ± 3.44 ng/mL vs. 17.18 ± 3.74 ng/mL, P<0.001). The average 25(OH)vitD levels were comparatively lower (17.11 ± 3.41 ng/ml) in children who had sepsis at admission, as opposed to other critically sick patient groups (21.04 ± 2.88). However, this difference did not reach statistical significance (P = 0.07). During their stay in the PICU, 10 patients, accounting for 10% of the total, unfortunately passed away. Although the average 25(OH) D levels were lower in the children who died compared to those who survived [19.44 ± 3.55 ng/ml vs. 21.05 ± 3.66 ng/ml], the difference did not have a statistically significant impact (P = 0.88). A comparison was made between the features of children who were low in Vitamin D and those who had appropriate levels, as shown in Table 2. There were no discernible gender disparities among the groups, while the patients with Vitamin D deficiency had advanced age and higher body weight. those with Vitamin D deficiency had a considerably higher median age compared to those with appropriate Vitamin D levels (P < 0.001).

The multivariable linear regression model shows that only patient age has a significant effect on the relative risk (RR) with a coefficient of -0.41 (95% confidence interval [CI]: -0.07 to -0.04; p < 0.001). The well-established risk variables of body mass index (BMI), gender, and underlying disorders did not show independent associations with vitamin D deficiency (VDD). The logistic regression analysis revealed that two covariates, catecholamine needs (OR: 42.55; 95% CI: 5.25–366.52; P = 0.002) and PRISM-III score (OR: 2.41; 95% CI: 1.22–2.63; P = 0.003), were substantially linked with death. The study did not find any association between mortality and other characteristics such as underlying disease, Vitamin D levels, requirement for mechanical ventilation, and presence of sepsis upon admission.[Table 3]

Table 1: ?

	Number	Percentage
Gender		
Male	62	62
Female	38	38
Age in Years		
below 2	40	40
2-6	30	30
6-12	28	28
Above 12	12	12
Mean Age	5.28±1.58	
Weight (kg)	22.85±2.69	
BMI (kg/m^2)	17.52±2.56	
Reason for PICU admission		
Neurological diseases	22	22
Acute respiratory infections	21	21
Sepsis	15	15
Trauma	13	13
Intoxications	12	12
Postoperative diseases	11	11
Others		
Underlying illness,	55	55
Mechanical ventilation, *n* (%)	55	55
PRISM III score	7.58±1.58	
PICU stay	5.25±2.14	
Catecholamine requirements, *n* (%)	35	35
Mortality *n* (%)	10	10

Table 2: Basic profile, clinical, and laboratory data in patients with or without Vitamin D deficiency

	25(OH)D				*P*
	≤20 ng/mL =70		>20 ng/mL=30		
	Number/ Mean	%	Number/ Mean	%	

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Gender					
Male	45	64.28	17	56.67	
Female	25	35.72	13	43.33	
Age in years	7.85±1.28		6.69±1.11		<0.001
Weight	23.58±2.96		21.58±2.54		<0.001
BMI (kg/m^2), median (IQR)	18.63±1.74		17.55±1.63		0.149
Main admission diagnosis, *n* (%)					
Neurological diseases	15	21.43	7	23.33	0.773
Respiratory track infections	11	15.71	10	33.33	0.076
Sepsis	10	14.28	5	7.14	0.328
Underlying diseases, *n* (%)	35	50	20	66.67	0.466
Mechanical ventilation *n* (%)	35	50	20	66.67	0.497
Catecholamine requirements, *n* (%)	22	21.43	13	43.33	0.034
PRISM-III score median (IQR)	7.58±1.31		6.54±1.44		0.211
PICU stay (days), median (IQR)	5.25±1.74		6.69±1.08		0.799
Mortality, *n* (%)	8	11.14	2	6.67	0.955
Total calcium (mg/dL)	9.42±0.89		9.78±0.96		<0.001
Phosphate (mg/dL)	4.22±1.16		4.55±1.22		0.095
Magnesium (mmol/L)	0.91±0.11		0.98±0.15		0.375
Ionized calcium (mg/dL)	3.37±0.77		3.58±0.88		0.173

Table 3: Multiple logistic regression

	OR	95% CI	*P*
Catecholamine requirements	42.55	5.25-366.52	0.002
PRISM-III score	2.41	1.22-2.63	0.003
Underlying diseases	4.18	1.67-14.63	0.07
Sepsis	1.96	1.21-5.71	0.24
Mechanical ventilation	6.96	1.47-54.85	0.08
Vitamin D deficiency	1.36	1.11-3.67	0.26

DISCUSSION

Based on the findings of this research, it is evident that a significant proportion (70%) of critically sick children had insufficient levels of Vitamin D (25[OH]vitD levels <20 ng/ml) at admission. The levels seen in this investigation are much more than the 40% rate reported in a previous study including 440 Turkish children and adolescents, aged 0 to 16 years, who visited the outpatient clinic.[15] The existing research indicates that the incidence of this condition in severely unwell infants ranges from about 30% to 84%.[16-21] The significant variations in the prevalence of VDD across various studies can be attributed to disparities in the populations under investigation, levels of sunlight exposure, weather conditions, dietary intake, Vitamin D supplementation, genetic variations in the proteins responsible for Vitamin D transportation, functioning, and metabolism, diverse measurement techniques for 25(OH)D, and varying threshold values.[22]

The current investigation has verified the previously established negative relationship between 25(OH)vitD levels and age. The findings from the present research indicate that the occurrence of Vitamin D deficiency (VDD) in patients admitted to the hospital during the autumn and winter seasons was much greater compared to sunnier months. In addition, the multivariable linear regression model found that only patient age and hospitalisation during the winter season were significantly linked to VDD. Similarly, studies have repeatedly shown that age, the season of the year, and dietary calcium consumption are variables that are consistently linked to 25(OH)vitD levels in healthy children.[23] Regrettably, the present investigation lacked any data pertaining to the calcium consumption of the youngsters.

Vitamin D has a physiological function in controlling immunity and regulating the activity of T- and B-cells, the generation of cytokines, and the expression of antimicrobial peptides.[24-26] The research findings indicated that patients diagnosed with sepsis upon admission had a comparatively lower level of 25(OH)D. However, it is important to note that this difference did not reach statistical significance. Madden et al,[16] showed that children who were hospitalised to the PICU with severe septic shock had lower levels of serum 25(OH)D compared to other severely sick children in the same unit. A separate research conducted in Ireland revealed that children who were referred to the PICU with suspected sepsis had lower levels of 25-hydroxyvitamin D (25(OH)D) compared to a control group. Furthermore, it was shown that insufficient levels of 25(OH)D were linked to the development of confirmed sepsis and unfavourable outcomes. The data collected from adults in a recent meta-analysis revealed a substantial rise in the risk of infection and sepsis.

Underlying medical conditions may cause a decrease in Vitamin D levels due to irregular dietary patterns, changed metabolic processes, or decreased exposure to UV radiation in the environment. Contrary to what was expected, the presence of underlying diseases did not have a substantial impact on the Vitamin D levels upon admission to the PICU, as seen in prior research on critically sick children.[16,17] No correlations were found between the level of Vitamin D and the PRISM III score in the present investigation. Similarly, many prior investigations have failed to establish any

ISSN (O): 2687-5365; ISSN (P): 2753-6556

correlation between Vitamin D deficiency (VDD) and severity score.[18,19,28] Nevertheless, McNally et al,[17] found that for each incremental point rise in PRISM III score, there was an 8% higher probability of VDD occurrence. Madden et al. reported a slightly similar finding, seeing an odds ratio (OR) of 1.19 (95% confidence interval [CI] 1.10-1.28) for a 1-quartile increase in PRISM III score per 5 ng/ml reduction in 25(OH)D levels. The lack of consistency in the correlation may be attributed to the diverse patient group across several studies and variability in the methods employed to evaluate the severity.

In addition, the present investigation found no discernible difference between the low and normal 25(OH)D groups in terms of the need for ventilation and length of stay in the PICU. This finding aligns with the findings published by Rippel et al,[18] and Rey et al,[19] Nevertheless, McNally et al,[17] and Sankar et al,[21] discovered that VDD is linked to an extended length of stay. The disparities across studies might be attributed to geographical and racial disparities, diverse causes for admissions to the Paediatric Intensive Care Unit (PICU), and variability in how children respond to acute stress and critical illness.

The discovery of a connection between Vitamin D levels and myocardial dysfunction, heart failure, and sudden cardiac death is a recent and significant finding.[29] The research findings indicate that individuals with VDD exhibited a significant increase in their need for catecholamines. Madden et al,[16] found that patients who were administered catecholamine had significantly lower levels of 25(OH)D compared to those who were not, with a median of 19.8 ng/ml vs 24.3 ng/ml ($P < 0.0001$). Additionally, there was a strong correlation between the use of vasopressors and a decrease in 25(OH)D levels ($r = 2.19$, $P < 0.0001$). In a similar manner, McNally et al,[17] observed that patients who needed catecholamine infusion had lower average levels of 25(OH)D (45 nmol/L vs. 38.5 nmol/L, $P = 0.006$). Previous research has shown that there is no correlation between Vitamin D deficiency and the need for catecholamine supplementation.[18,19] The present investigation did not find any substantial correlation between Vitamin D level and mortality. There was no difference in Vitamin D levels between survivors and nonsurvivors. Additionally, the logistic regression analysis showed that Vitamin D deficiency was not linked to death. Research conducted on adult individuals has shown an increased likelihood of death in people diagnosed with Vitamin D deficiency.[30] McNally et al,[17] discovered that during multivariate regression analysis, a 25(OH)D concentration below 50 nmol/L was autonomously linked to a PICU mortality rate of 1.5% (5 out of 326 patients), and all 5 patients who died had vitamin D deficiency.

CONCLUSION

Overall, it was observed that the prevalence of Vitamin D deficiency was significantly high among Indian children upon admission to the PICU. The individuals diagnosed with VDD had advanced age and higher body weight, and demonstrated a greater likelihood of receiving catecholamine treatment. There was no notable link seen between several indicators of sickness severity, such as death, and the amount of Vitamin D.

REFERENCES

1. Ashok A, ManjushaGoel, et al. Vitamin D level in critically ill children 6 months–5 years age admitted to intensive care unit in tertiary care hospital of Central India. Indian J Child Health. 2019;6(8).
2. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74(11):1498-513. doi: 10.1038/s41430-020-0558-y, PMID 31959942.
3. McNally JD, Nama N, O'Hearn K, Sampson M, Amrein K, Iliriani K, et al. Vitamin D deficiency in critically ill children: a systematic review and meta-analysis. Crit Care. 2017;21(1):287. doi: 10.1186/s13054-017-1875-y, PMID 29169388.
4. Yeşiltepe-Mutlu G, Aksu ED, Bereket A, Hatun Ş. Vitamin D status across age groups in Turkey: results of 108,742 samples from a single laboratory. J Clin Res Pediatr Endocrinol. 2020;12(3):248-55. doi: 10.4274/jcrpe.galenos.2019.2019.0097, PMID 31893581.
5. Wang L, Zhang C, Song Y, Zhang Z. Serum vitamin D deficiency and risk of gestational diabetes mellitus: a meta-analysis. Arch Med Sci. 2020;16(4):742-51. doi: 10.5114/aoms.2020.94433, PMID 32542074.
6. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007;7(9):684-700. doi: 10.1038/nrc2196, PMID 17721433.
7. Albanna E, Ali FY. Vitamin D and LL-37 in children with pneumonia. Egypt J Pediatr Allergy Immunol. 2010; 8:81-6.
8. Papandreou D, Malindretos P, Karabouta Z, Rousso I. Possible health implications and low vitamin D status during childhood and adolescence: an updated mini review. Int J Endocrinol. 2010; 2010:472173. doi: 10.1155/2010/472173, PMID 20011095.
9. He M, Cao T, Wang J, Wang C, Wang Z, Abdelrahim MEA. Vitamin D deficiency relation to sepsis, paediatric risk of mortality III score, need for ventilation support, length of hospital stay, and duration of mechanical ventilation in critically ill children: a meta-analysis. Int J Clin Pract. 2021;75(4):e13908. doi: 10.1111/ijcp.13908, PMID 33280208.
10. Ben-Eltriki M, Hopefl R, Wright JM, Deb S. Association between vitamin D status and risk of developing severe COVID-19 infection: a meta-analysis of observational studies. J Am Nutr Assoc. 2022;41(7):679-89. doi: 10.1080/07315724.2021.1951891, PMID 34464543.
11. Cariolou M, Cupp MA, Evangelou E, Tzoulaki I, Berlanga-Taylor AJ. Importance of vitamin D in acute and critically ill children with subgroup analyses of sepsis and respiratory tract infections: a systematic review and meta-analysis. BMJ, (Open). 2019;9(5):e027666. doi: 10.1136/bmjopen-2018-027666, PMID 31122993.
12. Jhang WK, Kim DH, Park SJ. Association of vitamin D deficiency with clinical outcomes in critically ill Korean children. Nutr Res Pract. 2020;14(1):12-9. doi: 10.4162/nrp.2020.14.1.12, PMID 32042369.
13. Aparna P, Muthathal S, Nongkynrih B, Gupta SK. Vitamin D deficiency in India. J Family Med Prim Care. 2018;7(2):324-30. doi: 10.4103/jfmpc.jfmpc_78_18, PMID 30090772.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

14. Jain V, Gupta N, Kalaivani M, Jain A, Sinha A, Agarwal R. Vitamin D deficiency in healthy breastfed term infants at 3 months & their mothers in India: seasonal variation & determinants. Indian J Med Res. 2011;133(3):267-73. PMID 21441679.
15. Andıran N, Çelik N, Akça H, Doğan G. Vitamin D deficiency in children and adolescents. J Clin Res Pediatr Endocrinol. 2012;4(1):25-9. doi: 10.4274/jcrpe.574, PMID 22394709.
16. Madden K, Feldman HA, Smith EM, Gordon CM, Keisling SM, Sullivan RM, et al. Vitamin D deficiency in critically ill children. Pediatrics. 2012;130(3):421-8. doi: 10.1542/peds.2011-3328, PMID 22869836.
17. McNally JD, Menon K, Chakraborty P, Fisher L, Williams KA, Al-Dirbashi OY, et al. The association of vitamin D status with pediatric critical illness. Pediatrics. 2012;130(3):429-36. doi: 10.1542/peds.2011-3059, PMID 22869837.
18. Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med. 2012;38(12):2055-62. doi: 10.1007/s00134-012-2718-6, PMID 23052958.
19. Rey C, Sánchez-Arango D, López-Herce J, Martínez-Camblor P, García-Hernández I, Prieto B, et al. Vitamin D deficiency at pediatric intensive care admission. J Pediatr (Rio J). 2014;90(2):135-42. doi: 10.1016/j.jped.2013.08.004, PMID 24184303.
20. Prasad S, Raj D, Warsi S, Chowdhary S. Vitamin D deficiency and critical illness. Indian J Pediatr. 2015;82(11):991-5. doi: 10.1007/s12098-015-1778-3, PMID 25967259.
21. Sankar J, Lotha W, Ismail J, Anubhuti C, Meena RS, Sankar MJ. Vitamin D deficiency and length of pediatric Intensive Care Unit stay: A prospective observational study. Ann Intensive Care. 2016;6(1):3. doi: 10.1186/s13613-015-0102-8, PMID 26745966.
22. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. Curr Opin Pharmacol. 2010;10(4):482-96. doi: 10.1016/j.coph.2010.04.001, PMID 20427238.
23. Gordon CM, Feldman HA, Sinclair L, Williams AL, Kleinman PK, Perez-Rossello J, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med. 2008;162(6):505-12. doi: 10.1001/archpedi.162.6.505, PMID 18524739.
24. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am. 2010;39(2):365-79. doi: 10.1016/j.ecl.2010.02.010, PMID 20511058.
25. Hewison M. Vitamin D and the intracrinology of innate immunity. Mol Cell Endocrinol. 2010;321(2):103-11. doi: 10.1016/j.mce.2010.02.013, PMID 20156523.
26. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. Chest. 2005;128(6):3792-8. doi: 10.1378/chest.128.6.3792, PMID 16354847.
27. Onwuneme C, Carroll A, Doherty D, Bruell H, Segurado R, Kilbane M, et al. Inadequate vitamin D levels are associated with culture positive sepsis and poor outcomes in paediatric intensive care. Acta Paediatr. 2015;104(10):e433-8. doi: 10.1111/apa.13090, PMID 26096884.
28. Ayulo M Jr., Katyal Ch, Agarwal Ch, Sweberg T, Rastogi D, Markowitz M, et al. The prevalence of vitamin D deficiency and its relationship with disease severity in an urban pediatric critical care unit. Endocr Regul. 2014;48(2):69-76. doi: 10.4149/endo_2014_02_69, PMID 24824802.
29. Makariou S, Liberopoulos EN, Elisaf M, Challa A. Novel roles of vitamin D in disease: what is new in 2011? Eur J Intern Med. 2011;22(4):355-62. doi: 10.1016/j.ejim.2011.04.012, PMID 21767752.
30. Arnson Y, Gringauz I, Itzhaky D, Amital H. Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients. Q J M. 2012;105(7):633-9. doi: 10.1093/qjmed/hcs014, PMID 22331959.

ISSN (O): 2687-5365; ISSN (P): 2753-6556