International Journal for Innovation Education and Research

ISSN: 2411-2933

The Use of Vitamin D in The Infectious Process in The Hospital Period in Childhood Effective?

Eliza Miranda Ramos;Matheus Dullius de Lima;Jéssica Eloy Cunha Gonzalez;Gilberto Gonçalves Facco;Elaine S. de P. Melo;Hugo Vieira Ramos;Francisco José Mendes dos Reis;Igor Domingos de Souza;Valter Aragão do Nascimento

Abstract

Goals: To verify whether the use of Vitamin D as parallel therapy to hospital and drug treatment can be effective in the process of infectious reduction in hospitalized children. Data source: This study is a systematic review and meta-analysis of randomized controlled trials, published between 2011 and the first quarter of 2019, in the Cochrane Library, Medline, US National Library of Medicine and the National Institute of Health (PubMed), Literature databases. Latin American and Caribbean Health Sciences (Lilacs), Scopus and Web of Science. The studies were scored by the Down and Black scale associated with the quality assessment method according to the Cochrane criteria (RCT). Summary of the data: Of the 1475 studies, 09 were included. There is a direct relationship between Vitamin D level and mortality rate in hospitalized children with infections. Conclusion: This study highlighted that the vitamin D deficiency in children under serum analysis during hospitalization triggers severe immunological changes.

Keyword: Vitamin D, Deficiency, Supplementation, Pediatrics, Hospitalization.

Published Date: 5/1/2020 **Page.364-377** **Vol 8 No 05 2020**

DOI: https://doi.org/10.31686/ijier.vol8.iss5.2351

The Use of Vitamin D in The Infectious Process in The Hospital Period in Childhood Effective?

Eliza Miranda Ramos[1,2,4], Matheus Dullius de Lima[3], Jéssica Eloy Cunha Gonzalez[2], Gilberto Gonçalves Facco[3], Elaine S. de P. Melo[1,2,4], Hugo Vieira Ramos[2], Francisco José Mendes dos Reis[1,2,4], Igor Domingos de Souza [1,2,4], Valter Aragão do Nascimento[1,2,4].

1 Post-Graduate Program in Health and Development in the Midwest Region, Federal University of Mato Grosso do Sul, Campo Grande, MS, Brazil.

2 Federal University of Mato Grosso do Sul, Campo Grande, MS, Brazil.

3 AnhangueraUniversity - UNIDERP, Campo Grande, MS, Brazil.

4 Group of Spectroscopy and Bioinformatics Applied to Biodiversity and Health, School of Medicine, Postgraduation Program in Health and Development in the Midwest Region.

Corresponding author: Eliza Miranda Ramos, Address: Francisco Serra - 147 - Vila Planalto. Campo Grande, MS. CEP - 79009040. Brazil. MS. E-mail: elizamirandaramos@gmail.com , Contact: 55 - 67 -999480071.

ABSTRACT

***Goals**: To verify whether the use of Vitamin D as parallel therapy to hospital and drug treatment can be effective in the process of infectious reduction in hospitalized children. **Data source:** This study is a systematic review and meta-analysis of randomized controlled trials, published between 2011 and the first quarter of 2019, in the Cochrane Library, Medline, US National Library of Medicine and the National Institute of Health (PubMed), Literature databases. Latin American and Caribbean Health Sciences (Lilacs), Scopus and Web of Science. The studies were scored by the Down and Black scale associated with the quality assessment method according to the Cochrane criteria (RCT). **Summary of the data:** Of the 1475 studies, 09 were included. There is a direct relationship between Vitamin D level and mortality rate in hospitalized children with infections. **Conclusion:** This study highlighted that the vitamin D deficiency in children under serum analysis during hospitalization triggers severe immunological changes.*

Keywords: Vitamin D, Deficiency, Supplementation, Pediatrics, Hospitalization.

1. INTRODUCTION

Improvement in survival of hospitalized children and critics infected by viruses or bacteria in the immune system in the hospital care and care process has been focused on the benefit of adjunctive therapies such as Vitamin D [1,2]. It is recognized that Vitamin D deficiency is common in critically ill hospitalized children, especially in intensive care [6,7]. Vitamin D is essential in bone structure and ideal in cardiovascular system and innate immune function [32]. Vitamin D deficiency has been associated in the last decade with an increased risk of progression of infectious diseases in the hospitalization process

[7-11]. Patients with levels of 20 ng/ml are usually categorized as hypovitaminosis D and treatment is started in children to prevent complications such as rickets [14-18]. Vitamin D deficiency is suggested by decreased Vitamin D intake and decreased sun exposure in about 60% of Brazilian children and the Brazilian child population has developed low Vitamin D (25(OH)D (<20 ng) levels/ml)[30,31]characterizing an epidemiological indicator in 15% with Vitamin D deficit in the Brazilian child population[18-21] this percentage increase in Vitamin D insufficiency in children has alarmed Brazilian health professionals even though others have questioned the clinical importance of Vitamin D insufficiency [22].

Increased Vitamin D deficiency has been associated with viral and bacterial respiratory infections and especially sepsis in children [24-26]. Vitamin D supplementation (1200UI) in the winter period has shown a marked decrease in the infectious process of influenza in some countries [27, 42] it has been previously shown that this deficit is related to the metabolization of Vitamin D (25 (OH) D) which produces hCAP-18 catelicidine an antimicrobial peptide [14-37]. Children in the hospitalization process under severe conditions such as sepsis have lower Vitamin D levels and are usually associated with lower catelicidine levels. [34, 37].

Hospitalization has generally been associated with higher levels of severely admitted illness in intensive care units (UTI) [22-38]. Low levels in the Vitamin D pre-hospitalization process and during admission to intensive care units are associated with short- and long-term causes characterized by mortality or bacteremia in children with severe conditions [22-30]. For this reason, this study aimed to verify whether the use of Vitamin D as a preventive therapy can reduce the infectious process in critically ill hospitalized children.

2. METHODS

2.1 PROTOCOL – This review was registered for publication in the International Prospective Register of Systematic Reviews - PROSPERO whose code was: CRD42019121732.

2.2 ELIGIBILITY CRITERIA – Eligible studies were considered randomized controlled trials that compared the use of Vitamin D in the infectious process in children in hospital treatment. The result of interest was the effect on the immune system through the clinical improvement of the child according to the Vitamin D supplementation dosage in the hospitalization process.

2.3 INFORMATION SOURCES – The research was conducted at the Cochrane Library, Medline Library, US National Library of Medicine and the National Health Institute (PubMed), Latin American and Caribbean Health Sciences Literature (Lilacs), Scopus, Web of Science, and Scientific Online Library (SCIELO). The latest survey was conducted in February 2019.

2.4 SEARCHS STRATEGIES – We use the following strategy for US National Library of Medicine and the National Institute of Health (PubMed)" Vitamin D" [MESH] or "Vitamin D Deficiency" AND "Infection" [MESH] And "Child" OR "Pediatrics" [MESH] OR "Child" AND "Hospitalization" OR "Inpatient" [MESH] OR "Supplementation AND Vitamin D". Variations of these strategies were used according to other sources required on certain platforms.

2.5 STUDY SELECTIONS AND DATA COLLECTION – Five researchers (E.M.R, M.D.d.L, G.G.F, J.E.C.G, C.A.S). Disagreements were resolved by consensus by a third reviewer (V.A.d.N). E.M.R performed data extraction and M.D.d.L confirmed extraction. For duplicate studies only the pre-cross-over result was included to eliminate the risk of biasing the residual effects of the specific methods used. A data extraction protocol was designed to collect relevant information from the studies used in this systematic review and meta-analysis including country, population sampling type, study design, Vitamin D Blood Serum dosage and key results. Some authors had to be contacted in order to obtain relevant information not included in the published studies.

2.6 QUALITY ASSESSEMENTS – This systematic review and meta-analysis included only studies that had comparison groups without systematic differences between the analyzed groups. Dosing in the Vitamin D supplementation process was considered randomized to the method, an indicator of high-quality study. If the groups were formed by other dosing means in Vitamin D supplementation, the baseline dose characteristics (time and dosage) were evaluated to determine if there was selection bias wich could favor any group. The study that did not meet quality control according to the established criteria was not included in this systematic review and meta-analysis. A review of the follow-up procedures in the Vitamin D supplementation process was performed at random to assess whether there was any performance bias in the included study. Blinding of participants in the groups was considered for evaluative quality of the studies, as these procedures are viable in experimental research.

2.7 DATA ANALYSIS – The primary outcome was standardization of Vitamin D dose differences in the supplementation process. For a better interpretation of dose-related efficacy in the Vitamin D supplementation process in hospitalized children, odds ratios were used (OR). The meta-analysis was performed by the Mante-Haenszel random effects model for each outcome variable (Vitamin D3 supplementation, clinical improvement (humoral response) and were presented with a 95% confidence interval (95% CI). Results heterogeneity was estimated by I^2 and publication bias risk tests were assessed by inspection of the asymmetric plotting funnel.

Table 01: Main features of the included studies.

Article Identification	Study Identification/ Country Year	Study Design	Population Sampling	Average Levels in Vitamin D Serum	Main Results
A	Rey C et al./Espanha/2015.	Randomized Study (02 weeks)	445 children.	19,2 ng/mL	Respiratory infection rates during hospitalization were less frequent in Vitamin D3, deficient patients, whereas renal infections and metabolic disorders were more frequent in Vitamin D3 deficient patients.

B	Jian Z et al./China/2018.	Randomized Study (16 weeks)	400 children.	20 ng/mL	Vitamin D3 has several immunomodulatory functions, which include up-regulation of antiviral peptides that are part of innate immunity and can inactivate viruses such as influenza.
C	Devi D et al./India/2014.	Randomized Study (01 weeks)	146 children.	20,0 ng/mL	Vitamin D3 level rates were statistically significant in the period of hospitalization; there is an efficiency of Vitamin D3 in the period of hospitalization both in the local and immune system. Hospitalized children show a significant drop in Vitamin D3 levels when hospitalized.
D	Raúl B.B. et al./Chile/2016.	Randomized Study (37 weeks)	90 children.	19,2 ng/mL	Children on admission with Vitamin D3 deficiency showed statistically significant elevation in blood lactate and procalcitonin
E	Spenta K. et al./Canada/2011.	Randomized Study (24 weeks)	97 children.	25 ng/mL	Children in the hospitalization period had elevated serum PTH in individuals with insufficient Vitamin D3. Vitamin D3 supplementation at doses of 800 IU to 1600 IU/day did not show an increase in $CD4_+$ in infected children. Vitamin D3 supplementation at 800 IU/day is inadequate in HIV children.
F	Piyush G. et al./ India/2016.	Randomized Study (24 weeks)	324 children.	12 ng/mL	Administration of Vitamin D3 supplementation at a single oral dose of 10.000 units/week showed no recovery from pneumonia, hospitalization duration and fever elimination time.
G	Joanna J. et al./Polônia/2018.	Randomized Study (12 weeks)	50 children.	20 ng/mL	There was a statistically significant change in induction of CD4 +, CD25+, Foxp3+. Vitamin D3 promotes the production of tolerogenic dendritic cells, which

					leads to the introduction of Foxp3+ regulatory cells. Vitamin D3 modulates active T-cell proteins by suppressing Th1 secretion.
H	Duygu O.H. et al./Turquia/2016.	Randomized Study (06 weeks)	74 children.	12 ng/mL	Children with optimal vitamin D3 levels had a medium level catelicidine in their urine. The frequency of Vitamin D3 deficit was significantly higher in cases of urinary tract infection. There is a high dependency ratio between Vitamin D3 deficit and ICU stay. Vitamin D3 has been recognized with effect on the urinary system, with immunomodulatory ability against Escherichia Coli infection. Proper dosage of Vitamin D may benefit the urinary tract during infectious periods by inducing catelicidine expression.
I	Galli E. et al./Itália/2015	Randomized Study (24 weeks)	89 children.	20 ng/mL	The active form of Vitamin D3 induces the expression of antimicrobial peptides that aid in the infectious process of the skin and immunosuppressive properties of the skin.

3. RESULTS

A total of 1475 articles were retrieved and nine articles were included in our review. All studies were randomized and placebo controlled which evaluated including 2693 children. The main features of the studies are shown in Figure 03.

A. STUDY CHARACTERISTICS – 87 studies were removed because they were duplicate, 1388 were recovered. Based on the title and summary these 1388 studies were selected for possible inclusion in the study, 375 were excluded for not reporting the presence of a placebo-controlled control group during the Vitamin D, 450 studies used children and adults in the surveyed sample, 356 studies did not use the dose of vitamin D supplementation in a randomized and informed manner, 188 studies did not

report primary results with the use of vitamin D in the infectious process. Nine articles were included in this systematic review and meta-analysis (TABLE 01).

B. QUALITY ASSESSEMENTS AND SIDE RISK – Quality assessment the result is shown in Table 02. Five articles met the full quality of the evaluation criteria in the inclusion process in this systematic review and meta-analysis (A, B, C, F, I). In all items analyzed, at least 70% of the studies had low risk of bias (FIGURE 01).

TABLE 02 – Quality risk of studies included according to Down and Black associated method according to Cochrane criteria (RCT).

Article Identification	Reporting (0 – 10)	External validity (0 – 03)	Internal validity – bias (0 – 07)	Confusion - bias of selection (0 – 06)	Power (0 – 5)	Total score
A	10	03	04	05	01	23
B	09	02	04	03	02	20
C	10	03	05	05	01	24
D	08	02	04	04	02	20
E	09	03	09	06	01	24
F	10	03	06	05	01	25
G	09	03	05	05	01	23
H	10	03	04	05	02	24
I	10	03	05	06	02	26

SOURCE: SARA, H. D.; BLACK, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol CommunityHealth.v.52. p.377–384. 1998.

Figure 01- Bias Risk Graph by type of bias assessed

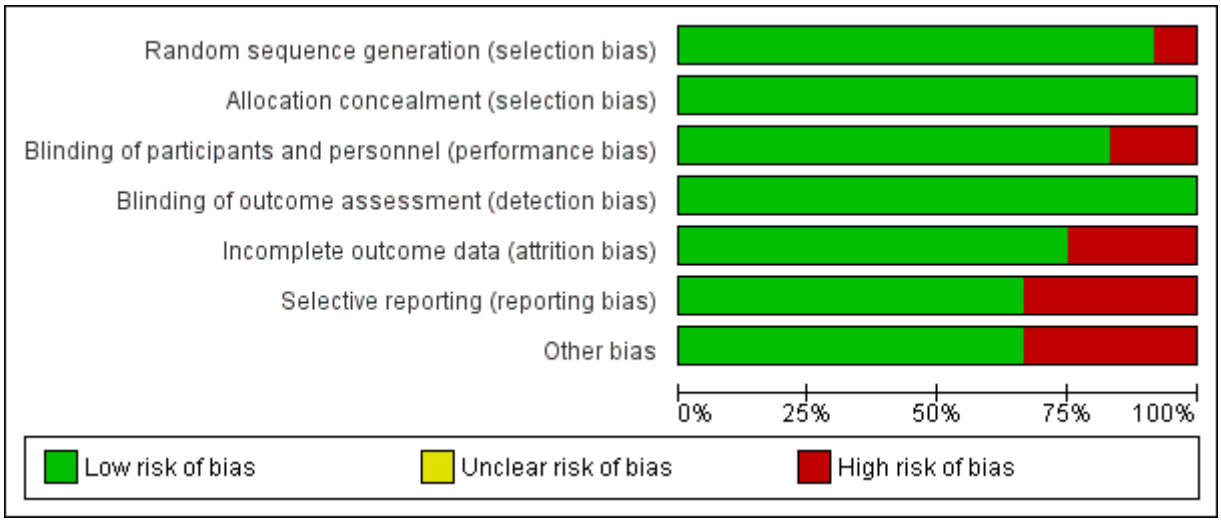


Figure 02 – Funnel graph with prevalence of chronic immunological severity (x-axis) by the standard error of each study (y-axis). Demonstrating heterogeneity between studies analyzed according to the effectiveness of Vitamin D3 and its relationship in the infectious process of hospitalized children.

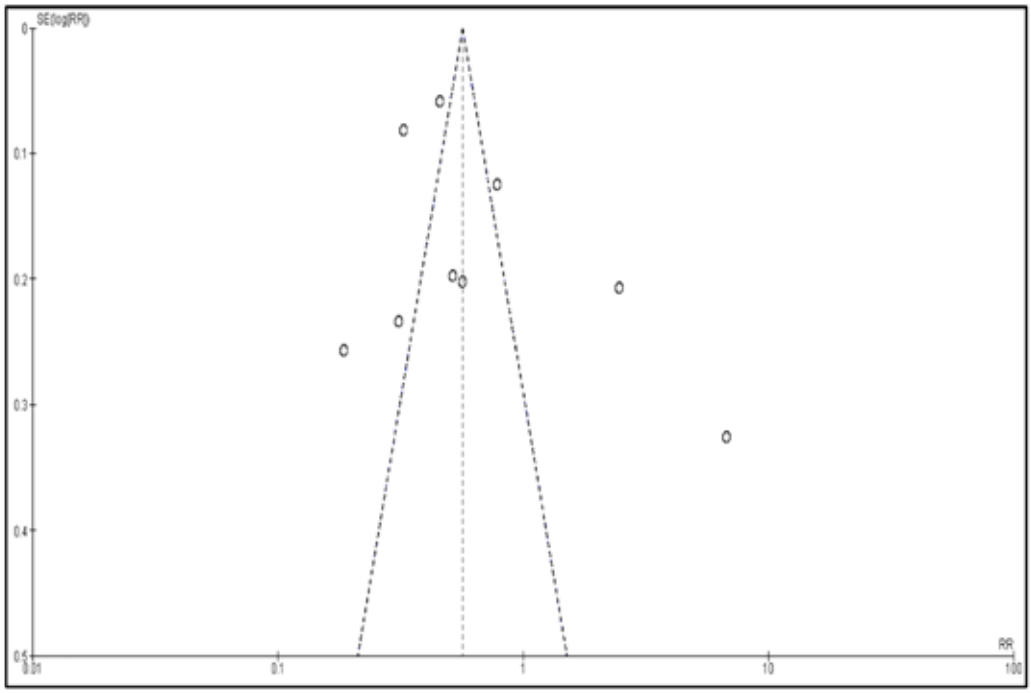
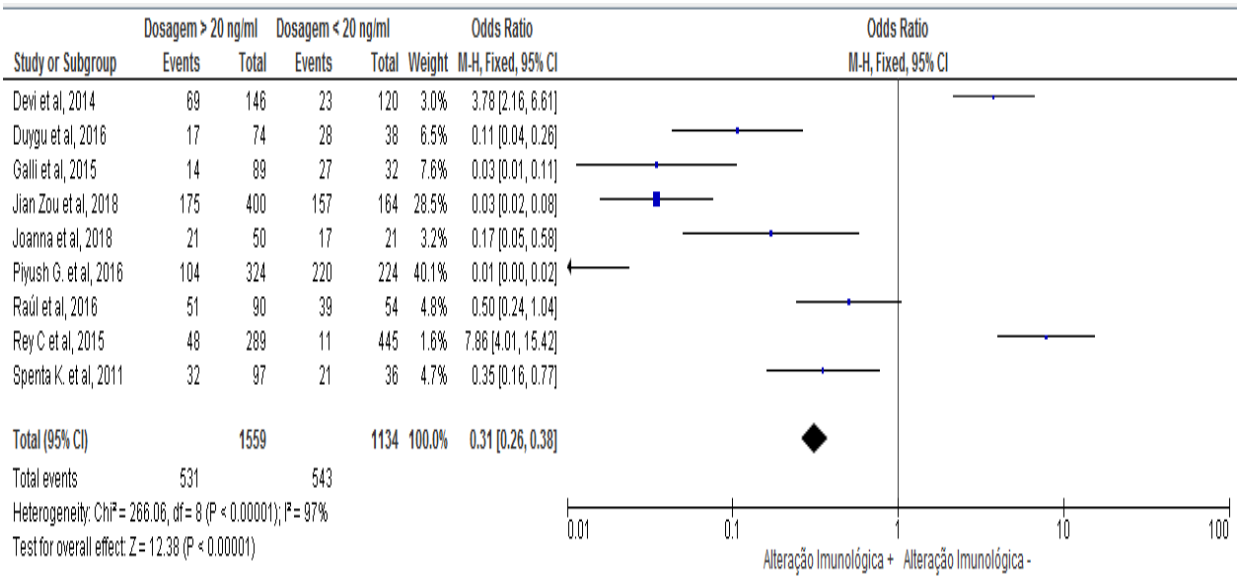


Figure 03 – Efficacy of clustering within confidence interval of risk ratio for Vitamin D3 dosage versus immunological changes in children.



The meta-analysis of the evaluated objectives (infectious process and supplemented dosage of Vitamin D) are show in Figure 3. While the final results and medium term results favored the reduction of

the infectious process with highs doses of Vitamin D as shown in Figure 02, the studies analyzed in this systematic review and meta-analysis confirmed that Vitamin D3 supplementation generates na efficient positive immune response in situations of hospitalization process. However, two studies [38-41] of Vitamin D3 supplementation in the present meta-analysis have not shown satisfactory or immunological protection outcomes during hospitalization [39,41].

Still in Figure 02, a total of 07 studies [A, B, D, E, F, G, H] reported a positive effect on immune attenuation after Vitamin D3 supplementation and this sensitivity analysis revealed that five studies were the contributors to these results [A, B, C, F, I] and no limitations in the quality assessment process were found in the studies. Heterogeneity was found in the final analysis results (12 = 97%), OR estimates were also statistically significant for incidence of improvement in the infectious process (OR = 0.35; CI = 95%: 0.16-0.77) which indicates improvement in the immune system in the infectious process as increased dosage in the Vitamin D supplementation process in hospitalized children compared to lower doses (OR= 7,86; IC 95%: 4,01-15,42).

Despite the small number of studies included in this meta-analysis to be examined, the assessed asymmetry of the funnel graph showed that there is no risk of publication bias (Figure 02).

4. DISCUSSION

Vitamin D3 supplementation had an effect on the total number of positive changes in immune defense cells (increase) when compared to the control group and the effect was statistically significant (p< 0,00001) [32-34]. Thus, the present systematic review and meta-analysis study suggests that Vitamin D3 supplementation has a significant immunomodulatory effect on the production of body defense cells (leukocytes, lymphocytes and plasma neutrophils for example) [34-41].

The articles reviewed in this systematic review and meta-analysis recently highlight that immune system cells express Vitamin D3 receptors and portray intracellular mechanisms capable of converting 25 (OH) D3 into their active formulation, in this case, 1.25 (OH) 2D3, Vitamin D3 has immunomodulatory function [36-42]. It can be seen from Graph 01 that in the studies analyzed in this systematic review and meta-analysis [34-42] Vitamin D3 supplementation was predominantly applied to the treatment groups to compare them with its application in control groups [42], therefor Vitamin D3 played na essential role in adaptive and innate immunity [36-41].

This functionality in the immune system occurs due to Vitamin D3-mediated activation through Toll-like receptors [36-42], where it increases resistance to human catelicidin antimicrobial peptide, reducing vulnerability to bacterial infections [36]. When comparing the dosage below 20 nmol/L, the selected studies showed an increase in the infectious process of the hospitalization period with an increase in the frequency of death with an infectious process [34,42].

This meta-analysis through Graph 01 shows a significant reduction in infectious process symptoms compared to children who did not supplement Vitamin D (Control Group) [34-42]. Graph 01 shows na increase in cell percentage baseline of CD4+, CD25+, and Foxp3+ during hospitalization in the groups compared to placebo, changes due to Vitamin D3e levels due to Vitamin supplementation D3[34-42].

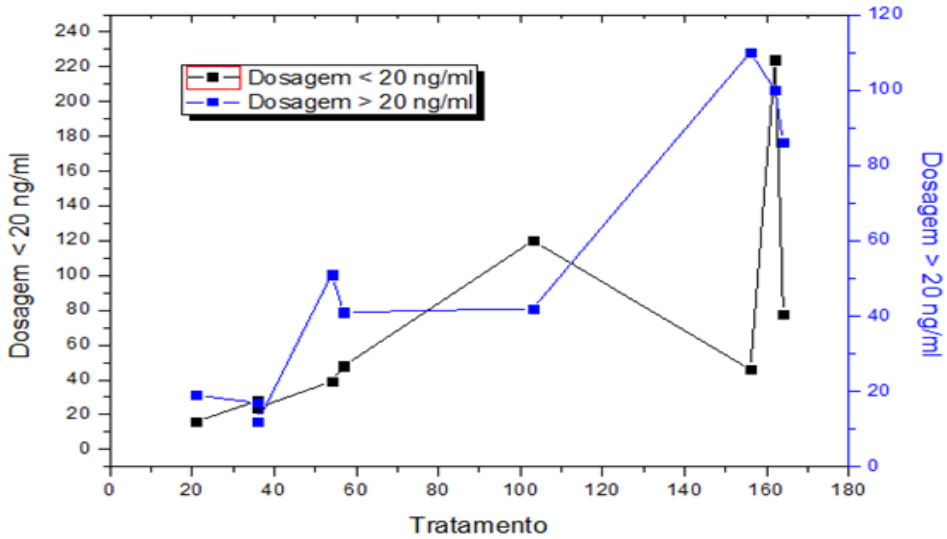
Vitamin D brings immunological improvement in the hospitalized child population by increasing serum IgA and IgG immunoglobulin levels [36-42] with peripheral increase in serum IgM levels in Vitamin D supplemented children. As well as na increase in serum catelicidin [36], an antimicrobial peptide responsible for immune boosting due to Vitamin D3 supplementation and significantly reduced the frequency of hospital complications such as pneumonia, sepsis or other infections [34-42].

In this systematic review and meta-analysis as shown in Figure 02, only a randomized, double-blind, placebo-controlled study used Vitamin D3 supplemented at a weekly oral dose of 100.000 units for children aged 6 months to 5 years.

In cases of respiratory infections and showed an increase in serum IgM levels in children supplemented with Vitamin D3 and serum catelicidine, and due to high Vitamin D3 supplementation there was an increase in na antimicrobial peptide which was responsible for the increase in reinforcement. Immune with Vitamin D Supplementation [36-40].

In this systematic review and meta-analysis study Graph 01 shows a potential beneficial effect of Vitamin D3 on CD4+ count, as the effects of Vitamin D3 include both immunostimulatory and immunosuppressive effects which may raise questions regarding dosage in this case > 1600 IU/ day may have unintended adverse consequences [34-42], so there is a need to continuously monitor active Vitamin D3 serum levels and immune function in hospital-infected patients who are supplemented with Vitamin D [34-40]

Graphic 1 – Monitoring of vitamin D3 serum levels in correlated supplementation in activation and immune function of pediatric patients infected in the hospital process.



This systematic review and meta-analysis study showed that a direct relationship between Vitamin D3 level and mortality, in this case low Vitamin D3 levels at admission, was directly associated with immunological worsening [34-42].

This systematic review and meta-analysis reinforced that patients admitted to intensive care units had a high incidence of hypovitaminosis D in all age groups, however the difference was statistically significant in older age groups, in this case children from 08 years to 13 years [39-42].

This study highlights that Vitamin D supplementation above 50000 IU/week is safe and protective against acute respiratory tract infections [34-42].

It is emphasized that Vitamin D has several immunomodulatory functions including the regulation of antiviral peptides that are part of human innate immunity and may, for example, inactivate influenza vírus [42].

5. CONCLUSION

This systematic review and meta-analysis found that the insufficient high prevalence of serum Vitamin D in a hospitalized infant patient triggers severe immune system changes, as well as decreased bacterial defense sequelae and an association with increased length of hospital stay and infectious process and a growing death toll.

However, Vitamin D supplementation shows evidence of improvement in clinical status and immune response, with an increase in serum IgA and IgG Immunoglobulin levels, especially serum catelicidin, reducing hospital complications such as pneumonia, sepsis and other infections.

6. DATA AVAILABILITY

The data used to support the findings of this study are included within the article.

7. CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this paper.

8. ACKNOWLEDGMENTS

This research was partially supported by the Brazilian Research Council (CNPq) This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES).

REFERENCES

1. ADORINI L, PENNAG. Control of autoimmune diseases by the vitamin D endocrine system. Nature Clinical Practice Rheumatology. v. 4. p.404-412. 2008.

2. ALVESFS, FREITAS FG, BAFI AT, AZEVEDO LC, MACHADO, FR. Concentração sérica de vitamina D e disfunção orgânica em pacientes com sepse grave e choque séptico. Revista brasileira de terapia intensiva. v.27. n.04. p.376-382. 2015.

3. BUISON AM, KAWCHAK DA, SCHALL J, OHENE-FREMPONG K, STALLINGS VA, ZEMEL BS. Low vitamin D status in children with sickle cell disease. J Pediatr. v.145. p.622-627.2004.

4. BUCHOWSKI MS, TOWNSEND DW, WILLIAMS R, CHEN KY. Patterns and energy expenditure of free-living physical activity in adolescents with sickle cell anemia. J Pediatr. v.140. p.92. 2002.

5. BERWICK M, KESLER D. Ultraviolet radiation exposure, vitamin D, and cancer. Photochemistry and Photobiology, v.81. n.6. p.1261-6. 2005.

6. HOLICK MF. Vitamin D deficiency. The New England Journal of Medicine. v.357. n.3. p.266-81. 2007.

7. CARNEIRO J, MURAD Y. Crescimento e Desenvolvimento. In: Agência Nacional de Vigilância Sanitária, editor. Manual de diagnóstico e tratamento de doenças falciformes. Brasília: ANVISA; 2002. p. 77-82.

8. DE SOUZA KC, DAMIÃO JJ, SIQUEIRA KS, DOS SANTOS LC, DOS SANTOS MR. Nutritional follow-up of children with sickle cell anemia treated in a primary care unit. Rev Paul Pediatr. 2008; 26: 400-4.

9. DE-LA-TORRE-UGARTE-GUANILO MC.; TAKAHASHI RF.; BERTOLOZZI M. R. Revisão sistemática: noções gerais. Revista da Escola de Enfermagem USP. v. 45, n. 5, p. 1260 - 1266, out. 2011.

10. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement - PRISMA Group. PLoS Med. v.6. n.7. p.e1000097. 2009.

11. ZIPITIS CS, AKOBENG, AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Archives of Disease Childhood. v.93. p.512-517. 2008.

12. PONSONBY AL, PEZIC A, ELLIS J, MORLEY R, CAMERON F, CARLIN J, DWYER T. Variation in associations between allelic variants of the vitamin D receptor gene and onset of type 1 diabetes mellitus by ambient winter ultraviolet radiation levels: a meta-regression analysis. American Journal of Epidemiology. v.168. p.358-365. 2008.

13. SANTOS CMC, PIMENTA CAM, NOBRE MRCN. A estratégia PICO para a construção da pergunta de pesquisa e busca de evidências. Revista latino-americana de enfermagem. v.15. n.3. 2007.

14. VELDMAN CM, CANTORNA MT, DELUCAHF. Expressão do receptor 1,25-dihidroxivitamina d (3) no sistema imune. Arco. Biochem. Biofísica. v.374, p.334-338. 2000.

15. ZMUDA JM, CAULEY JA, FERRELL RE. Molecular epidemiology of vitamin D receptor variants. Epidemiol Rev. v.22, p.203–17. 2000.

16. ROLF L, MURIS AH, THEUNISSEN R, HUPPERTS R, DAMOISEAUX J, SMOLDERS J. Vitamin D3 supplementation and IL-02/IL-2R pathway in multiple sclerosis: attenuation of progressive disturbances? Journal of Neuroimmunology. v.314. p.50-57. 2018.

17. KRIEGEL MA, MANSON JE, COSTENBADER KH. Does vitamin D affect risk of developing autoimmune disease? a systematic review. Semin Arthritis Rheum. v.40, p.512-31, e8. 2011.

18. SEARING DA, ZHANG Y, MURPHY JR, HAUK PJ, GOLEVA E, LEUNG DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. J Allergy Clin Immunol. v.125, p.995-1000. 2010.

19. MISRA M, PACAUD D, PETRYK A, COLLETT-SOLBERG PF, KAPPY M. Drugand Therapeutics Committee of the Lawson Wilkins PediatricEndocrine Society Vitamin D deficiency in children and its management:review of current knowledge and recommendations.Pediatrics. v.122, p.398-417. 2008.

20. ZAGO MA, PINTO AC. The pathophysiology of sickle cell disease: from the genetic mutation to ultiorgan disfunction. Rev Bras HematolHemoter. v.29, p.2007-14. 2007.

21. FIXLER J, STYLES L. Sickle cell disease. PediatrClin N Am. v.49, p.1193-210. 2002.

22. MITCHELL MJ, KAWCHAK DA, STARK LJ, ZEMEL BS, OHENE-FREMPONG K, STALLINGS VA. Brief report: parent perspectives of nutritional status and mealtime behaviors in children with sickle cell disease. J Pediatr Psychol. v.29. p.315-20. 2004.

23. KAWCHAK DA, SCHALL JI, ZEMEL BS, OHENE-FREMPONG K, STALLINGS VA. Adequacy of dietary intake declines with age in children with sickle cell disease. J Am Diet Assoc. v.107, p.843-8. 2007.

24. ROVNER AJ, STALLINGS VA, KAWCHAK DA, SCHALL JI, OHENE-FREMPONG K, ZEMEL BS. High risk of vitamin D deficiency in children with sickle cell disease. J Am Diet Assoc. v.108, p.1512-6. 2008.

25. LEE P, EISMAN JA, CENTER JR. Vitamin D deficiency in critically ill patients. The New England Journal of Medicine. v.360. n.18. p.1912-4. 2009.

26. SOLIMAN HM, MERCAN D, LOBO SS, MÉLOT C, VINCENT JL. Development of ionized hypomagnesemia is associated with higher mortality rates. Critical Care Medicine. v.31. n.4. p.1082-7. 2003.

27. ROSS AC, MANSON JE, ABRAMS, SA, ALOIA JF, BRANNON PM, CLINTON SK, RAMON A, DURAZO-ARVIZUJ, CHRISTOPHER GR,RICHARD LG, GLENVILLE J, CHISTOPHER, SK, SUSAN TM, CLIFFORD JR, SUE AS. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. The Journal of Clinical Endocrinology & Metabolism. v.96. n.1. p.53-8. 2011.

28. NIERMAN DM, MECHANICK JI. Bone hyperresorption is prevalent in chronically critically ill patients. Chest. v.114. n.4. p.1122-8. 1998.

29. VANDEN BG, VAN RD, VANHOVE P, WOUTERS PJ, DE POURCQ L, BOUILLON R. Bone turnover in prolonged critical illness: effect of vitamin D. The Journal Clinical Endocrinology & Metabolism. v.88. n.10. p.4623-32. 2003.

30. VENKATRAM S, CHLIMURI S, MUHAMMAD A, SALAKO A, MADANMOHAN P, DIAZ-FUENTES G. Vitamin D deficiency is associated with mortality in the medical intensive care unit. Crtical care. v.15. n. R292. p.07-09. 2011.

31. SARA H D, BLACK, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology & Community Health. v.52. p.377–384. 1998.

32. GALLI, LRR, CARELLO PG, GIAMPIETRO P, PANEI PM. Serum Vitamin D levels and Vitamin D supplementation do not correlate with the severity of chronic eczema in children. Eur Ann Allergy Clin Immunol. Vol47, N2, 41-47, 2015.

33. REY C, DAVID SA, JESÚS LH, PABLO MC, IRENE GH, BELÉN P, ZAMIR P. Vitamin D deficiency at pediatric intensive care admission. J Pediatria. v.90, n.2, p.

36. PIYUSH G, POOJA D, DHEERAJ S, NISHA S, NIDHI B, IQBAL RK, AJAY KB, SV M. Vitamin D Supplementation for Treatment and Prevention of Pneumonia in Under-five Children: A Randomized Double-blind Placebo Controlled Trial. INDIAN PEDIATRICS. v.53, 2016.

37. SPENTA KMBBS, ETIENNE BS, MB CHB, DEREK S, ESTHER A, STANLEY ER, ARI BMD. Vitamin D Supplementation and CD4 Count in Children Infected with Human Immunodeficiency Virus. THE JOURNAL OF PEDIATRICS. Vol. 159, No. 6. December 2011.

38. SARA HD, BLACK N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health.v.52. p.377–384. 1998.

39. RAÚL BBA, IVÁN RN, RUBÉN PZ, GONZALO SG. Déficit de vitamina D nos cuidados intensivos pediátricos. Rev Chil Pediatr. v.87, n.6, p.480-486. 2016.

40. DEVI D, SURESH K, NARESH S, RAKESH K, MEENU S, SUNIT S. Fall in Vitamin D Levels during Hospitalization in Children. International Journal of Pediatrics. Article, 6 pages. 2014.

41. JIAN Z, JUAN D, LETING H, YOUCHENG W, YIMEI S, HAILONG L. Preventive Effects of Vitamin D on Seasonal Influenza A in Infants: A Multicenter, Randomized, Open, Controlled Clinical Trial. The Pediatric Infectious Disease Journal. v.37. n.8. 2018.