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REVIEW ARTICLE
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Effects of vitamin D in the prevention of acute viral bronchiolitis: systematic review

Efeitos da vitamina D na prevenção da bronquiolite viral aguda: revisão sistemática

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ABSTRACT

Aims: Published evidence suggests that Vitamin D supplementation may have a protective effect on infectious disease of the lower respiratory tract. The objective of this review was to critically appraise the effects of vitamin D intake in the prevention of acute viral bronchiolitis in children.

Methods: We searched the databases Medline, EMBASE, Web of Science, LILACS, and Cochrane Central Register of Controlled Trials, until December 2014, using the keywords: "Vitamin D" or cholecalciferol or ergocalciferol and "bronchiolitis, viral" or "viral bronchiolitis" or "bronchiolitides, viral" or "viral bronchiolitides". Studies evaluating the effect of vitamin D intake in the prevention of acute viral bronchiolitis in young children were included. Studies with less than two weeks of intervention and review articles were excluded.

Results: The search identified 241 articles, among which 20 articles were selected for full reading and two articles were included in the systematic review, comprising 296 children. No study measured serum levels of vitamin D. One of the included studies was a clinical trial, where the number of episodes of acute viral bronchiolitis was significantly lower in children supplemented with vitamin D (Group I: mean 0.6±0.7 Group II: mean 1.4±0.9; P=0.001). The other, a case-control study, did not find a significant relationship between the occurrence of acute viral bronchiolitis cases and the intake of vitamin D (odds ratio 1.7, 95% confidence interval 0.7-4.0).

Conclusions: Current scientific evidence is insufficient to prove clinical benefits of vitamin D in preventing acute viral bronchiolitis.

KEY WORDS: vitamin D; bronchiolitis, viral; infant; child.

RESUMO

Objetivos: Evidências publicadas sugerem que a suplementação da vitamina D pode ter efeito protetor nas infecções do trato respiratório inferior. O objetivo desta revisão foi avaliar os efeitos da ingestão de vitamina D na prevenção da bronquiolite viral aguda em crianças.

Métodos: Foram feitas buscas nas bases de dados Medline, EMBASE, Web of Science, LILACS e Cochrane Central Register of Controlled Trials, até dezembro de 2014, usando os descritores "Vitamin D" ou cholecalciferol ou ergocalciferol e "bronchiolitis, viral" ou "viral bronchiolitis" ou "bronchiolitides, viral" ou "viral bronchiolitides". Foram incluídos estudos que avaliaram o efeito da ingesta da vitamina D na prevenção da bronquiolite viral aguda em crianças. Estudos com intervenção menor que duas semanas e artigos de revisão foram excluídos.

Resultados: A busca identificou 241 artigos, entre os quais 20 artigos foram selecionados para leitura na íntegra e dois artigos foram incluídos na revisão sistemática, incluindo 296 crianças. Nenhum estudo mediu os níveis **séric**os de vitamina D. Um dos estudos incluídos foi um ensaio clinico, no qual o número de episódios de bronquiolite foi significativamente menor nas crianças suplementadas com vitamina D (Grupo I: média 0,6±0,7 Grupo II: média 1,4 ±0,9; P=0,001). No outro, um estudo de casos e controles, não se encontrou relação significativa entre casos de bronquiolite viral aguda e ingesta de vitamina D (*odds ratio* 1,7 – intervalo de confiança 95% 0,7-4,0).

Conclusões: As evidências científicas atuais são insuficientes para comprovar os benefícios clínicos da vitamina D na prevenção da bronquiolite viral aguda.

DESCRITORES: vitamina D; bronquiolite viral; lactente; criança.

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Abbreviations: AVB, acute viral bronchiolitis; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

INTRODUCTION

Acute viral bronchiolitis (AVB) is the most common lower respiratory tract infection (LRTI) in children up to two years of age [1-3]. It is one of the main reasons for visits in pediatric emergency rooms [3,4], and it is the cause of approximately 17% of hospital admissions at this age [5,6]. According to the Clinical Practice Guideline from the American Academy of Pediatrics, there are annually 100,000 admissions caused by AVB in the United States, with an estimated cost of 1,730 million dollars [7].

The discovery of vitamin D receptors in the nucleus of cells in the immune system enabled research aimed at identifying the role of vitamin D in the homeostasis of the immune system and in disease prevention [4]. Some of these studies suggested that vitamin D supplements could prevent respiratory infections such as AVB [8-10].

There is evidence that vitamin D activates anti-microbial function in monocytes and macrophages, helping to protect against infectious diseases and acting to keep the integrity of the innate immune system, changing the activity of T lymphocites, regulatory and natural killer cells [11,12].

Vitamin D is synthesized in the skin after solar radiation or it is obtained in small amounts in food rich in vitamin D (eg, milk and fish) [4]. As it is a shortly available nutrient and exposure to sunlight varies according to the individual's habits, latitude and time of the year, the prevalence of vitamin D deficiency is not rare [6,13]. There is no consensus regarding the optimum level of vitamin D, but most researchers adopt the reference values suggested by Holick in 2007, who considered levels of 25-hidroxivitamin D <20 ng/ml (50 nmol/L) as deficiency (6). The American Academy of Pediatrics currently recommends 400 daily IU of vitamin D from the first days of life up to adolescence [14].

In 2013 McNally et al. [15] published a meta-analysis appraising the relation between the polymorphism of the vitamin D receptors in bronchiolitis caused by respiratory syncytial virus (RSV), finding a positive relation between the FokI polymorphism and severe bronchiolitis by RSV [15]. Bergman et al. [16] performed a meta-analysis, which included 11 studies with a total of 5,660 participants, providing evidence that supplement with vitamin D reduced significantly the risk of infections of the respiratory tract (odds ratio [OR] 0.64; 95% confidence interval [CI] 0.49-0.84; p=0.0014). Likewise, it provided evidence that doses of vitamin D given every day are associated to the reduction of LRTI (OR 0.51, 95% CI 0.39-0.67), however, this effect was not evident when vitamin D supplement was given in large doses or in bolus such as once a month (OR 0.86, 95% CI 0.62-1.20) [16]; this study reviewed infections of the respiratory tract in general, not appraising AVB separately.

Such information is of great public interest because should the effectiveness of vitamin D in preventing bronchiolitis be proven, vitamin D supplementing could become a low cost intervention with a comprehensive impact on children's health. This systematic review was aimed at appraising the intake of vitamin D to prevent AVB in children.

METHODS

The systematic review followed the criteria suggested in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [17]. The protocol of this review was registered in PROSPERO (CRD42014014971) database.

We searched the following databases: Medline, EMBASE, Web of Science, LILACS, and Cochrane Central Register of Controlled Trials, (CENTRAL, The Cochrane Library), until December 2014. The search was also performed in references of the reviewed articles, and in the "grey literature" (eg, data found in institutional repositories, webpages, proceedings, technical reports). Furthermore, the subject of the research was discussed with a specialist in the area of investigation. No sort of limitation regarding language, age or study type whatsoever was included imposed.

The combination of the following terms was used in the search strategy: "Vitamin D" or cholecalciferol or ergocalciferol and "bronchiolitis, viral" or "viral bronchiolitis" or "bronchiolitides, viral" or "viral bronchiolitides". The complete search results are available as a supplementary document on the web page.

Studies evaluating the effect of vitamin D intake in the prevention of AVB in children were included. Studies with intervention shorter than two weeks, review articles, experimental models and editorial letters were excluded. The studies were selected by two reviewers who independently assessed the eligibility criteria of the studies. At first, the titles and abstracts of the articles were read, and then those that matched the eligibility criteria for review were read in full. Any discrepancies between the reviewers

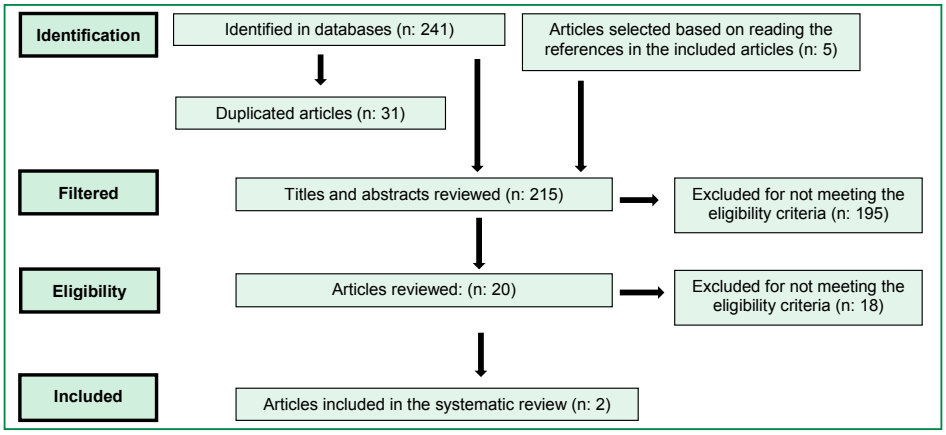

Figura 1. Flowchart of selection of the articles included.

regarding the inclusion of studies were solved with an appraisal by a third reviewer. After being selected, the articles that met the selection criteria were read in full, and the following data was extracted from those that remained in the study: authors, journal, year of publication, location, participants' age, recruiting method, study methodology (blinding, others), sample size, participants' follow-up time, number of eligible intervention groups, and, for each intervention group: dosage, period, frequency, co-intervention, as well as data on the magnitude of the effect of such intervention.

We appraised as primary endpoint events of AVB and as secondary endpoint cases of bronchiolitis that needed hospital admission and/or progressed to death. The quality of the included studies was assessed using the tools for assessing risk of bias from Cochrane Collaboration. The following quality criteria were used: sequence generation method; concealing assignments; blinding both participants and evaluators; incomplete data; and selective choice of endpoints.

RESULTS OF SELECTION

We identified 241 articles from the search: 41 articles from Pubmed, 162 from EMBASE, 38 from Web of Science, zero articles from LILACS and zero articles from Cochrane Central Register of Controlled Trials. After reading the articles in full, only two of them [18,19] met the inclusion criteria of the study (**Figure 1**).

CONTENT OF THE REVIEW

Considering the two articles that met the eligibility criteria, one is an observational study of the case-control type [18], and one is a non-randomized clinical essay with intervention [19]. From the selected studies we have a total of 296 participants, from both sex, aging between 0-5 years between 2007-2012. Both studies excluded infants with co-morbidities such as prematurity, heart disease, babies from complicated pregnancies, children with atopies and babies from mothers who have received medication during pregnancy. The studies were conducted respectively in Egypt and Canada. In the study by Leis et al. [18], the children caretakers were given food record questionnaires, with no follow-up on the participants of the study. The study by El-Mazary et al. [19] assessed vitamin D supplementing in the first six months of life, conducting monthly appointments with anamnesis, physical examinations and diagnostic tests when necessary (**Table 1**).

Table 1. Characteristics of the studies included.

First Author Magazine	Location/Year	Type of study	Participants	Ages	Measurement Vitamin D	Participants' follow-up	Effect magnitude
Leis KS Translational Pediatrics	Canada, 2012	Case-control study	197 children Cases (105) Controls (92)	0-5 years	Food record	No follow-up	OR 1.7 (95% confidence interval 0.7 to 4.0)
El-Mazary AAM Egypt J Pediatr Allergy Immunol	Egypt, 2012	Clinical essay Does not describe any type of randomization or blinding	99 children Group I (n: 48) Group II: (n: 51)	Newborns and infants	Group I: supplemented with vitamin D 400 IU in the first 6 months Group II: Not supplemented	Intervention period: 6 months. Monthly medical evaluation.	mean±standard deviation Group I: 0.6±0.7 Group II: 1.4±0. 9 P=0.001

No study included in this review measured vitamin D in the participating children. Leis et al. [18] applied a questionnaire estimating vitamin D intake in children with and without a diagnostic of AVB. The study did not demonstrate a significant relation between the levels of vitamin D and prevalence of AVB (OR 1.7, 95% CI 0.7-4.0) [18]. In contrast, the study by El-Mazary et al. [19] demonstrated that the incidence of respiratory infections was significantly lower in children supplemented with vitamin D during the first six months of life than in those who did not received this supplement (Group I: mean 0.6±0.7 Group II: mean 1.4±0.9; P=0.001).

In the study by Leis et al. [18] there was no loss of patients, and it presented a high risk of bias in the selection, as participants in the control group were children without respiratory symptoms. In spite of patients' assignment, the data are not sufficient to determine this type of bias; this study also does not report if there was blinding of the participants' caretakers, of nurses and evaluators. Regarding the endpoints, there was little loss of participants in both groups, and data loss was balanced between them, with similar chances for data loss [18].

Regarding the assessment of risk of bias in the study by El-Mazary et al. [19], clinical essay, it was not clearly described the type of randomization, assignment, blinding both participants and evaluators. The criteria for the diagnostic of AVB was also not clearly defined. There is no report of significant data loss [19].

In neither study there were reports of deaths secondary to AVB, as there was not increase or decrease in the amount of hospital admissions of patients who received vitamin D supplement [18,19]. In spite of evidence of reduced incidence of respiratory infections with vitamin D intake, there is no enough evidence demonstrating its effect on the prevention of AVB.

DISCUSSION

The findings of the study by El-Mazary et al. [19], in infants who lived in urban areas and with dark skin (factors that increase the incidence of vitamin D deficiency due to less exposure to sunlight), agree with a randomized double blind study performed in 2012, with adults who had immunodeficiency, which demonstrated that vitamin D intake reduced the risk of acute LRTI, frequent in the winter [20] R. In addition to these studies, there are other evidences such as a prospective cohort study conducted by Belderbos et al. [21], which demonstrated that healthy newborns with vitamin D deficiency had an increased risk for LRTI, especially AVB caused by RSV in the first year of life. Recently, two systematic reviews demonstrated that vitamin D intake reduced significantly the risk of respiratory tract infections; however, these reviews did not assess the direct association between vitamin D and AVB [16,22].

There is also lack of evidence regarding the adequate dosage of vitamin D intake to prevent LRTI, especially AVB. In the study by El-Mazary et al. [19], they used a dose of 400 IU/day, which is currently recommended by the American Academy of Pediatrics [14]. Regarding pneumonia, in 2010 Manaseki-Holland et al. [23] demostrated that children between 1 and 36 months of age, with a diagnostic of pneumonia, who received supplement with a single oral dose of 100,000 IU of vitamin D, along with the use of antibiotics, were less susceptible to recurrent pneumonia 90 days after the intervention. However, Martineau [24] published a study with children between 1 and 11 months who received quarterly doses of 100.000 IU (bolus) of vitamin D, demonstrating that these children presented higher recurrence of pneumonia/year (0.06 vs 0.04). According to that study, fast increase of vitamin D is capable of suppressing adaptive responses to the infection [24]. The meta-analysis by Bergman et al. [16] demonstrated that the interval and the dosage of vitamin D are an important factor to be considered, as there is evidence that daily doses of vitamin D present a better therapeutic effect than doses given in bolus.

One of the major limitations of this systematic review is the lack of included studies; nevertheless, the study search was not restricted by language, type of study, methodology of assessment of the levels of vitamin D in none of the data bases used, for a larger representativeness of the available evidence. Therefore, current scientific evidence is insufficient to prove clinical benefits of vitamin D in preventing AVB, but still the recommendations of the main pediatric guidelines include vitamin D supplementation for children less than two years of age due to other benefits.

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