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Relationship between vitamin d levels and intestinal dysbiosis in children/adolescents a systematic review protocol

Relação entre os níveis de vitamina d e disbiose intestinal em crianças/adolescentes: protocolo de revisão sistemática
Relación entre los niveles de vitamina d y la disbiosis intestinal en niños/adolescentes un protocolo de revisión sistemática

RESUMO

A insuficiência de vitamina D desencadeia reações imunogênicas no intestino e na disbiose. Objetivo: este protocolo descreverá os métodos de uma revisão sistemática que sumará estudos que examinaram a relação entre os níveis de vitamina D e disbiose intestinal em crianças e adolescentes. Método: uma revisão sistemática será desenvolvida nas buscas de artigos em cinco bases de dados. Como critérios de inclusão, estudos observacionais ou experimentais analisando a associação entre a os "níveis de vitamina D" e "disbiose". O processo de seleção e extração dos dados será realizado por dois revisores de forma independente. O risco de viés e o nível de evidência serão analisados, aplicando a ferramenta de avaliação Joana Brigs Institute (JBI). Os dados serão sintetizados usando metanálise com efeitos randômicos quando os resultados apresentaram suficiente homogeneidade. Resultados: a síntese de alta qualidade e ou análise descritiva das evidências atuais serão fornecidas a partir da associação dos níveis de vitamina D e a relação com a disbiose. Conclusão: Este estudo poderá fornecer evidências sobre a relação entre os níveis de vitamina D e disbiose em crianças e adolescentes.

DESCRIPTORES: Criança; Vitamina D; Aptidão Física; Disbiose

ABSTRACT

Vitamin D insufficiency triggers immunogenic reactions in the intestine and dysbiosis. Objective: This protocol will describe the methods of a systematic review that will summarize studies that have examined the relationship between vitamin D levels and intestinal dysbiosis in children and adolescents. Method: a systematic review will be developed in the search for articles in five databases. As inclusion criteria, observational or experimental studies analyzing the association between "vitamin D levels" and "dysbiosis". The data selection and extraction process will be carried out by two reviewers independently. The risk of bias and the level of evidence will be analyzed using the Joana Brigs Institute (JBI) assessment tool. Data will be synthesized using meta-analysis with random effects when the results showed sufficient homogeneity. Results: High quality synthesis and/or descriptive analysis of current evidence will be provided from the association of vitamin D levels and the relationship with dysbiosis. Conclusion: This study may provide evidence on the relationship between vitamin D levels and dysbiosis in children and adolescents.

DESCRIPTORS: Child; Vitamin D; Physical Fitness; Dysbiosis

RESUMEN

La insuficiencia de vitamina D desencadena reacciones inmunogénicas en el intestino y disbiosis. Objetivo: Este protocolo describirá los métodos de una revisión sistemática que resumirá los estudios que han examinado la relación entre los niveles de vitamina D y la disbiosis intestinal en niños y adolescentes. Método: se desarrollará una revisión sistemática en la búsqueda de artículos en cinco bases de datos. Como criterios de inclusión, estudios observacionales o experimentales que analicen la asociación entre "niveles de vitamina D" y "disbiosis". El proceso de selección y extracción de datos será realizado por dos revisores de forma independiente. El riesgo de sesgo y el nivel de evidencia se analizarán mediante la herramienta de evaluación del Joana Brigs Institute (JBI). Los datos se sintetizarán mediante metanálisis con efectos aleatorios cuando los resultados muestren suficiente homogeneidad. Resultados: Se proporcionará una síntesis de alta calidad y / o un análisis descriptivo de la evidencia actual a partir de la asociación de los niveles de vitamina D y la relación con la disbiosis. Conclusión: este estudio puede proporcionar evidencia sobre la relación entre los niveles de vitamina D y la disbiosis en niños y adolescentes.

DESCRIPTORES: Niño, Vitamina D, Aptitud Física, Disbiosis.

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INTRODUCTION

Recently, vitamin D has been associated with a wide range of biological activities. Among the role of vitamin D in the maintenance of intestinal homeostasis, vitamin D is capable of stabilizing interepithelial junctions and promoting an adequate balance between the intestinal microbiota and intestinal immunity.^{1,2}

Vitamin D can be obtained through exposure to sunlight, food intake and supplementation. The liver enzyme vitamin D 25-hydroxylase converts vitamin D to its main circulating form, 25-hydroxyvitamin D [25(OH)D]. Subsequently, 25(OH)D is converted to its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D] by the renal cytochrome P450 enzyme, 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1). The expression of this limiting enzyme is not restricted to the kidney, but has also been described in other types of cells, including keratinocytes, osteoblasts, chondrocytes and macrophages.³

This wide distribution of CYP27B1

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outside the kidney supported its role beyond calcium homeostasis, phosphate and even immunomodulation. The biological activity of 1,25(OH)2D is mediated by a member of the nuclear hormone receptor family, the vitamin D receptor (VDR), which is expressed copiously in the small and large intestines.^{4,5,6}

The lumen of the human intestine, especially the colon, contains a large amount of commensal, symbiotic and pathogenic bacteria. A harmful inflammatory response in the gut can be attenuated by the mucus layer and the underlying epithelium, working together to limit the entry of bacteria or their immunogen products into the interstitium. Microbial dysbiosis and the entry of immunogenic material into the interstitium can activate innate and adaptive immune cells, the main immunological effects on the development and duration of IBD (Inflammatory Bowel Disease). Mounting evidence indicates that vitamin D/VDR signaling plays a beneficial role in IBD. In general, impaired VDR signaling is associated with the inflammation and mucosal damage seen in IBD; whether defecti-

ve VDR signaling causes or is the effect of bowel disease is unclear.^{7,4,8}

However, the current consensus states that vitamin D supplementation tends to prevent or resolve the inflammatory response and minimize disease progression. Despite these deficiencies, it is currently recommended to monitor and normalize vitamin D status in patients with IBD.^{9,10}

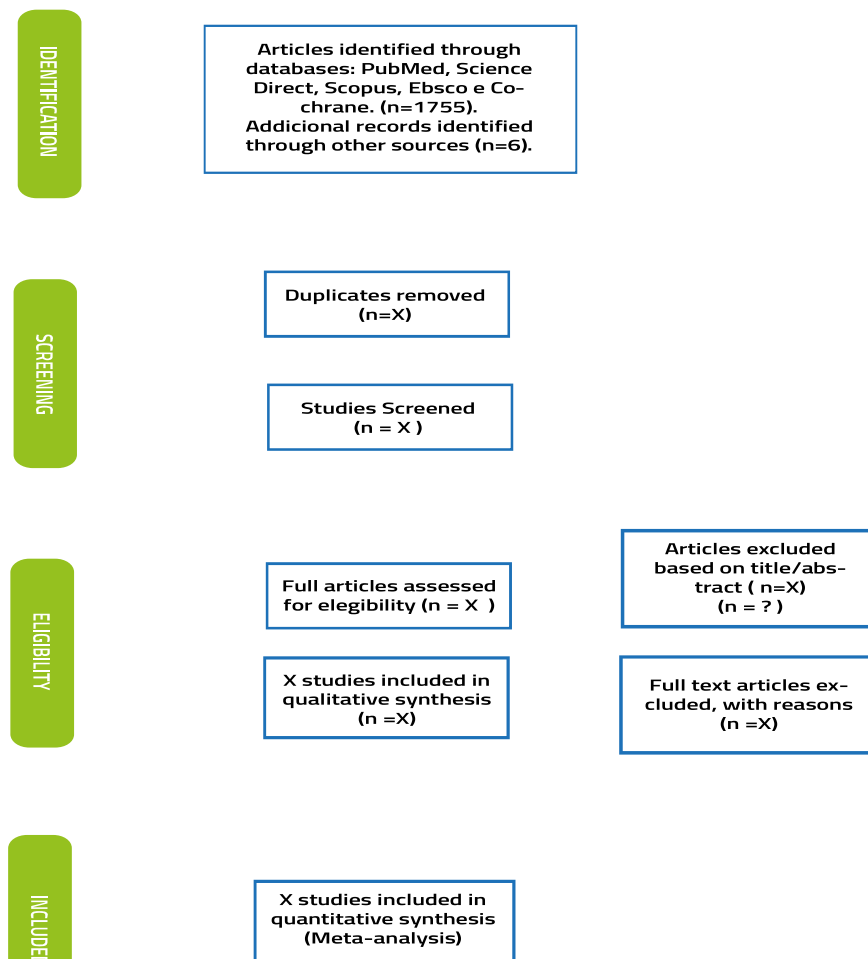
Vitamin D has been used as a health reference in children and adolescents, due to its potentialized interaction in the immune system, acting as a protective substance of the vascular endothelium, endocrine tissue, protection of the intestinal endothelium, in addition to immunomodulator of and contributes to the regulation of blood glucose and as an endocrine stimulant of the parathyroid.^{8,11} Therefore, this protocol aimed to describe the methods of a systematic review that will summarize studies that have examined the relationship between vitamin D levels and intestinal dysbiosis in children and adolescents.

METHODS

This protocol followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline 12 and registered in the International Prospective Registry of Systematic Reviews (<http://crd.york.ac.uk/PROSPERO>) CRD42020196566.

Electronic searches will use the following databases: PubMed, Science Direct Database, Scopus Database, Ebsco Information Service and Cochrane Library. The following descriptors were combined with the medical subjects (MeSH): "Child"[Mesh] OR (Children) OR "Adolescent"[Mesh] OR (Adolescents) OR (Adolescence) OR (Teens) OR (Teen) OR (Teenagers) OR (Teenager) OR (Youth) OR (Youths) OR (Adolescent, Female) OR (Adolescent, Female) OR (Adolescent, Male) OR (Adolescent, Male) OR (Adolescent, Male) OR (Male Adolescent) OR (Male Adolescents) AND "Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR (Calcio) OR ((3 beta,5Z,7E)-9,10-Secocholesta-5,7,

Figura 1 - Prisma Flow



Fonte: The PRISMA Group

10(19)-trien-3-ol) OR (Vitamin D 3) OR (Vitamin D3) OR (Cholecalciferols) AND "Dysbiosis"[Mesh] OR (Dysbioses) OR (Disbiosis) OR (Dysbiosis) OR (Dys-symbiosis) OR (Dys symbiosis) OR (Dys symbiosis) OR (Dysbacteriosis) OR (Dysbacteriosis) OR (Disbacteriosis) OR (Dysbacteriosis).

We will also search reference lists of relevant studies and reviews and manually search gray literature such as study records. Studies related to the effects of physical fitness programs on children will be included in this systematic review and if the results demonstrate whether they are homogeneous, a meta-analysis will be performed, as well as randomized controlled trials (RCTs),

controlled clinical trials (CCTs), comparative and retrospective prospective cohort studies, cluster trials, cross-sectional studies and observational studies. We will try to seek as many studies as possible due to the lack of original research on vitamin D and dysbiosis in children and adolescents. Detailed information about the PubMed search strategy is shown in Figure 1.

Studies that include individuals aged 9 to 17 years old, being white, black and non-Indian, with no gender limit, no limit on the year of publication of the study and no language restriction, are eligible. Animal studies are ineligible; books, book chapters, monographs, dissertations, theses, literature review articles, case studies or abstracts

will be excluded from the research; published studies with adults, elderly, pregnant women; children or adolescents with autoimmune, genetic and neuropsychiatric diseases.

The first step, the search in the databases and the selection of titles, abstracts and articles will be carried out by two researchers independently, considering the inclusion and exclusion criteria. In case of disagreement among researchers, a third reviewer was consulted in the consensus meetings. All steps of the system review were performed manually Figure 1.

For the second stage, the extraction of a standardized form will be used by two reviewers for this step independently, and disagreements between them must be resolved with the help of a third reviewer. Detailed extraction information is as follows: first author, year of publication, country of publication, study design, sample characteristics, number of participants, and outcomes. We will endeavor to contact the authors of the corresponding study by email to resolve any missing data.

The Cochrane Bias Risk Tool 14 with item generation of: random sequencing, allocation concealment, masking, incomplete outcome data, selective reporting, and other biases will be used to assess the quality of the included studies. Otherwise, Joan Briggs (JBI) 14, which includes consideration of patient selection, study comparability and outcome assessment, will be used to assess the quality of non-randomized studies.

As treatment measures, Review Manager V.5.4 software 14 will be used to conduct the meta-analysis if the data turns out to be homogeneous. Effect measures were defined as: prevalence ratio or odds ratio and respective confidence intervals. In longitudinal studies: relative risk or odds ratio and respective confidence intervals, based on evidence between vitamin D levels and intestinal dysbiosis in children and adolescents. All these data will have a confidence interval of 95%, if there is a possibility of non-homogeneous data, a systematic narrative review will be carried out.

Taking into account the possibility of

lack of data and/or need for more information about the studies, we will contact the corresponding author by email and, if doubts persist, we will analyze the existing data, assuming them as lost.

For heterogeneity analysis will be evaluated by Q test and I² statistic with RevMan 5.4. 1 Parameters to quantify research heterogeneity:

0% - 30% - not important, 31% - 60% - moderate heterogeneity, 61% - 80% - Substantial heterogeneity and 81% - 100% - considerable heterogeneity.

The evaluation bias will be through the creation of funnel charts, whereas a symmetric funnel chart indicates a low risk of bias, while an asymmetric funnel chart indicates a high risk of bias.

DISCUSSION

Innate and adaptive immunity are interrelated with the maintenance of intestinal homeostasis. Studies describe that vitamin D and its receptor play a key role in activating immunomodulatory cells, such as dendritic cells, lymphocytes, and types of T cells. 6,7,8

Intestinal dysbiosis can be the result of alterations in the intestinal microbiome and in the intestinal immune system, mediated by environmental factors, in a context of implicit genetic susceptibility. In particular, the remarkable increase in lifestyle habits, hypovitaminosis D over time and geographic patterns of incidence suggest that environmental exposures to the sun are important in the risk of developing intestinal dysbiosis in children and adolescents. 5,3,6,16

Exposure of the skin to the sun is the most important source of vitamin D in many places, through endogenous synthesis. Both sun exposure and vitamin D have profound effects on immune function that may be relevant to the development of intestinal dysbiosis in children and adolescents. 4,8

There is evidence that low sun exposure and/or hypovitaminosis D are associated with an increased risk of dysbiosis and perhaps exacerbation of the disease. We fo-

cus primarily on intestinal dysbiosis, where the effects of specific environmental factors can be seen more clearly, and a history of genetic susceptibility. 11,9,17

The impact of vitamin D on T cells and its relevance to the emergence of dysbiosis have been described. In general, vitamin D suppresses Th1/Th17 cells while promoting T reg cells. This scenario allows a T cell-mediated immune response to clear microbes from the affected area resulting in dysbiosis. 12,15,16,17

Thus, it is essential that more robustness and plausibility occur in relation to the amount of evidence on the subject, a fact that highlights the importance of this review.

CONCLUSION

This study may provide evidence on the relationship between vitamin D levels and dysbiosis in children and adolescents, as significantly vitamin D and its receptor are closely involved in the maintenance of intestinal homeostasis from the epithelium to the regulation of intestinal biota and mediation of activation of the cells of the innate and adaptive immune system, which in turn will contribute to possible healthy behavior behaviors for this transitional age group, considering collective health at world levels.

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