RELATIONSHIP BETWEEN 25(OH) D LEVELS AND DYSBIOSIS IN CHILDREN - SYSTEMATIC REVIEW

ABSTRACT
Objective: We systematically analyzed the relationship between 25(OH)D serum levels and intestinal dysbiosis in children. Methods: The following databases were systematically searched: Pubmed, Embase, Lilacs, Scopus, Ebsco, and Cochrane. Two reviewers independently examined the studies, collected data, assessed the risk of bias, and ranked the levels of evidence for each outcome in the studies. The pre-specified parameters of interest were 25(OH)D serum levels; sex and intestinal dysbiosis. We only included data from peer-reviewed articles in our analyses. Results: In our primary analysis, there was a positive trend between serum 25(OH)D <20 ng/ml and intestinal dysbiosis, this result should be interpreted with caution. In this systematic review, we identified two observational studies (n=330) with poor quality evidence in which insufficient serum levels of 25(OH)D showed a direct relationship with the occurrence of intestinal dysbiosis, the relationship of intestinal dysbiosis with sufficient levels of Vitamin D is not based on solid evidence. Conclusions: We await the results of ongoing studies to determine this effectiveness.
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**Keywords:** Calcitriol; dysbiosis; child; adolescent.

**RESUMO**
Objetivo: analisamos sistematicamente a relação entre os níveis séricos de 25(OH)D e a disbiose intestinal em crianças. Métodos: foram pesquisadas sistematicamente nas seguintes bases de dados: Pubmed, Embase, Lilacs, Scopus, Ebsco e Cochrane foram pesquisadas até 10 de fevereiro de 2023 e sem restrição de idioma. Dois revisores examinaram os estudos, coletaram dados, avaliaram o risco de viés e classificaram os níveis de evidências para cada resultado nos estudos, independentemente. Os parâmetros de interesse pré-especificados foram níveis séricos de 25 (OH)D; sexo e disbiose intestinal. Incluímos apenas dados de artigos revisados por pares em nossas análises. Resultados: em nossa análise primária, houve uma tendência positiva entre 25(OH)D sérico <20 ng/ml e disbiose intestinal, esse resultado deve ser interpretado com cautela. Nesta revisão sistemática, identificamos dois estudos observacionais (n=330) com evidências de baixa qualidade nos quais os níveis séricos de 25(OH)D insuficientes apresentaram uma relação direta com a ocorrência de disbiose intestinal, a relação da disbiose intestinal com níveis suficientes de vitamina D não é baseada em evidências sólidas. Conclusões: aguardamos os resultados dos estudos em andamento para determinar essa eficácia.

**Palavras-chave:** Calcitriol; disbiose; criança; adolescente.

**RESUMEN**
Objetivo: analizamos sistemáticamente la relación entre los niveles séricos de 25(OH)D y la disbiosis intestinal en niños. Métodos: se realizaron búsquedas sistemáticas en las siguientes bases de datos: Pubmed, Embase, Lilacs, Scopus, Ebsco y Cochrane hasta el 10 de febrero de 2023 y sin restricciones de idioma. Dos revisores examinaron de forma independiente los estudios, recopilaron datos, evaluaron el riesgo de sesgo y calificaron los niveles de evidencia para cada resultado de los estudios. Los parámetros de interés preespecificados fueron los niveles séricos de 25(OH)D; sexo y disbiosis intestinal. En nuestros análisis sólo incluimos datos de artículos revisados por pares. Resultados: En nuestro análisis primario, hubo una tendencia positiva entre la 25(OH)D sérica <20 ng/ml y la disbiosis intestinal; este resultado debe interpretarse con precaución. En esta revisión sistemática, identificamos dos estudios observacionales (n=330) con evidencia de baja calidad en los que los niveles séricos insuficientes de 25(OH)D presentaron una relación directa con la aparición de disbiosis intestinal, la relación entre la disbiosis intestinal y los niveles suficientes de La vitamina D no se basa en evidencia sólida. Conclusiones: Se esperan los resultados de los estudios en curso para determinar esta eficacia.

**Palabras clave:** Calcitriol; disbiosis; niño; adolescente.

1. Introduction

25(OH)D, a known metabolite of vitamin D, has an established function in the skeletal muscle system as well as a fundamental role in modulating the immune response. It is suggested that the adequate status of 25(OH)D contributes to protection against infectious diseases, intestinal dysbiosis,
autoimmune and cardiovascular diseases, diabetes mellitus, and neurocognitive dysfunctions, it is observed that low serum concentrations of 25(OH)D are related to risk of development and progression of these diseases (Han YP. et al, 2013; Dimitrov V, White JH. 2017; Mori B et al, 2022).

Research in recent years has emphasized the importance of the gut microbiome and its association with health and the immune system. In general, 25(OH)D signaling can activate innate immunity and simultaneously suppress adaptive immunity (Chow EC. Quach HP. Vieth R. Pang KS. 2013). On the other hand, the gut microbiome, as a symbiotic community, is critical to maintaining host metabolic homeostasis. Intestinal dysbiosis is related to metabolic syndrome, and type 2 diabetes (Tilg H, Cani PD, Mayer EA. 2016). This review sought to systematically examine the research on the Relationship between Serum 25(OH)D Levels and Intestinal Dysbiosis in Children.

2. Methods

The research was designed using the Cochrane collaboration recommendations for systematic reviews and reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA, 2020). The initial selection was based on the titles and the abstract of manuscripts. The eligible articles were analyzed and the reference lists of them were evaluated. These steps were performed independently and conducted by two pairs of reviewers (BM/CMS), and the other pair helped when there were disagreements (JFMB). This systematic review was registered in PROSPERO (International Prospective Register of Systematic Reviews) in November 2021, with registration number CRD42020196566.

Electronic searches were performed in MEDLINE (via PubMed), EMBASE (via ScienceDirect), Scopus, EBSCO, and Cochrane, in addition to manual searches in the references of included studies and in non-indexed records. The following descriptors were used: The search will be done by the following terms: child or Preschool OR Adolescents OR Adolescence OR Teens OR Teen OR Teenagers OR Teenager OR Youth OR Youths OR Adolescents Female OR Adolescent Female OR Female Adolescent OR Female Adolescents OR
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Adolescents Male OR Adolescent Male OR Male Adolescent OR Male Adolescents) AND (Vitamin D OR Cholecalciferol OR Hydroxycholecalciferols OR Ergocalciferol OR 25-Hydroxyvitamin D OR Dihydrotachysferol) AND (Dysbiosis OR Dysbacteriosis OR Dysbiose OR Dysbiosis OR Disbioses OR Dysbiosis OR Dysbioses OR Dys-symbiosis OR Dys symbiosis OR Dys- symbioses OR Dysbacteriosis OR Dysbacterioses OR Disbacteriosis OR Disbacterioses intestinal OR intestine OR intestinal microbiota).

Inclusion and exclusion criteria are as follows the acronym "PEO" was used to assess study eligibility criteria. (P) participants: children and adolescents, (E) Exposition: children who have dysbiosis. (O) outcome: vitamin D levels. Articles published until December 2022 were included. Studies that were not available in full in any database and that were not found after attempts to contact the authors were excluded, as well as articles published in non-roman characters.
3. Results

A total of 330 records were initially identified by searching electronic databases (Figure 1). After removing 20 duplicates, the titles and abstracts of 310
articles were screened, 15 of which were selected for reading in full. After this stage, 2 articles were eligible for analysis, comprising longitudinal studies. No study was retrieved through the manual search. This review included two (02) cross-sectional studies that comprehensively analyzed 218 children and adolescents. Serum 25(OH)D levels were compared with intestinal dysbiosis in both studies. The general results outlined that the serum levels of 25 (OH)D are significantly reduced when there is intestinal dysbiosis in children.

4. Quality assessment

The quality assessment of the included studies was performed using the GRADEpro® tool, which contains three domains for cross-sectional studies: Effect magnitude, Presence of dose-response gradient, and Residual confounding factors (Kuusi T. 2018; BMJ. 2020). The two observational studies included in our review were classified as low levels of evidence. The above review was performed by two independent reviewers (BM and CM) with disagreement resolved by a third reviewer (JFMB).

Table 1- Characterization of studies included in the systematic review, February 2023

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Participants Follow-up</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirect evidence</th>
<th>Inaccuracy</th>
<th>Publication bias</th>
<th>Overall certainty of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>218 (2 Observational studies)</td>
<td>Not severe</td>
<td>Grave</td>
<td>Not severe</td>
<td>Grave</td>
<td>Strong dose-response gradient association</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

Fonte: GRADEpro (2022)

4. Discussion

This is the first systematic review conducted that relates serum 25(OH)D levels with intestinal dysbiosis in children and adolescents, observational studies have recorded the occurrence of 25(OH)D insufficiency levels globally (Hewison M. 2010; Holick MF. et al, 2011). However, 25(OH)D insufficiency is more common in children, and low 25(OH)D levels are associated with various

In this study, we evaluated, through a systematic review, whether 25(OH)D levels are related to dysbiosis in children and adolescents. We found data from 02 (two) studies involving representative samples of Qatari and South Korean children and adolescents. The main findings were: i) scarcity of research establishing the causal relationship between 25(OH)D serum levels and intestinal dysbiosis involving children younger than 12 years old; ii) the predominantly used measurement instruments are self-reported questionnaires and some have validation data.

The importance of the intestinal microbiota in the pathogenesis of dysbiosis is well known, and marked reductions in microbial diversity have been reported in patients with intestinal dysbiosis and that could be related to a decrease in the expression of vitamin D receptors (VDR). VDRs appear to be an important immune regulator in the gut biota, whose deficiencies result in dysbiosis of the gut microbiome (Wu S. et al., 2010, Wu S. et al, 2015, Park SW. et al, 2021).

These results suggest that intestinal dysbiosis, related to a decrease in VDR expressions, is a more sensitive factor in children when compared to adults (Wu S. et al, 2015; Park SW. et al, 2021, Singh P. 2022, Fatemi A. et al, 2016). Recent studies have demonstrated the gut-liver axis, which links the gut microbiota to VDRs. It is primarily due to the increased exposure and susceptibility of the liver to changes in the gut microbiome, as it receives 70% of its blood supply from the gut via the portal vein (Hamza FN. et al, 2023). Furthermore, this association is believed to be due to increased generation of bacterial-derived endotoxins or downregulation of junctional proteins leading to disruption of the intestinal barrier and translocation of toxins to extra-intestinal tissues (Baur K. et al, 2012; Cosnes J. et al, 2011 Han YP. et al, 2004). Notably, intestinal permeability and the prevalence of intestinal bacterial overgrowth are increased (Dimitrov V, White JH, 2017).

Gut microbiota also releases Toll-like receptor (TLR) ligands such as TLR2, TLR4, and TLR9. These are pathogen-associated molecular patterns (PAMPs) in humans and in promoting pro-fibrotic pathways (Tilg H, Cani PD,
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Mayer EA. 2016; Li J, Cordero P, Nguyen V, Oben JA. 2016; Borrelli A. 2018). However, only two studies (Park SW. Lee YJ, Ryoo E. 2021; Singh P. 2022) investigated the relationship between serum 25(OH)D levels and Intestinal Dysbiosis in our review. However, it has been shown that the bioavailability of serum 25(OH)D in the intestinal lumen can impact intestinal dysbiosis as well as health in different ways, and analyzing this relationship is important, as the correlates, determinants, and impacts on health are different (Dimitrov V, White JH. 2017; Bakke D, Sun J. 2018; Spedding S. et al., 2013; Ananthakrishnan AN. 2014; Ungaro R, 2016; Akimbekov NS. et al., 2020).

This updated review reinforces that most children and adolescents have reduced serum levels of 25(OH)D, the vitamin D receptor (VDR) is ubiquitous in tissues and may contribute to the transport of 25(OH)D from other tissues. These results address some important issues that directly affect the bioavailability of 25(OH)D when intestinal dysbiosis occurs. Constant efforts must be made to advance the understanding and measurement between serum 25(OH)D levels and intestinal dysbiosis in children and adolescents; understand the impact on the health of this population of children and adolescents; and simultaneously investigate qualitative and quantitative information on the relationship between 25(OH)D levels and intestinal dysbiosis in children and adolescents to improve the accuracy of our monitoring and intervene in what makes sense.

5. Conclusion

In conclusion, evidence indicates that intestinal 25(OH)D and VDR levels play a key role in intestinal homeostasis through their effects on the intestinal microbiota itself. There are mutual interactions between 25(OH)D levels, VDR, and the gut microbiome that have yet to be fully elucidated. Our review suggests that sufficient 25(OH)D levels may represent a regulatory factor for inflammation and the production of antimicrobial peptides which, in turn, are responsible for remodeling the bacterial communities that make up the intestinal microbiota of children and adolescents.

These factors (inflammation and microbiota composition) are implicated in intestinal dysbiosis; Although the complex regulatory network that controls each
of these aspects still needs to be fully elucidated, our findings are important not only for a better understanding of intestinal dysbiosis but may also have applicability of the evidence to other diseases where the host is in contact with bacteria and innate and adaptive immune responses as in intestinal dysbiosis.

6. Study Limitations

The present study was limited to investigating the relationship between Vitamin D levels and dysbiosis in children; therefore, other problems related to 25 (OH)D were not the subject of this study. Another limitation of this study is that only two of the studies had a control group. Thus, our systematic review was carried out without comparison with another group. For more robust results, controlled studies are needed.

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