International Journal of Advanced Engineering Research and Science (IJAERS)
Peer-Reviewed Journal
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-9, Issue-4; Apr, 2022
Journal Home Page Available: https://ijaers.com/
Article DOI: https://dx.doi.org/10.22161/ijaers.94.16

Influence of vitamin D deficiency on intestinal dysbiosis: A systematic review

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Received: 15 Feb 2022,

Received in revised form: 03 Apr 2022,

Accepted: 10 Apr 2022,

Available online: 21 Apr 2022

***Keywords*— Dysbiosis, Vitamin D deficiency, Gastrointestinal microbiome.**

***Abstract*—** *The intestinal microbiota influences important local and systemic processes for the organism, having in its composition probiotic bacteria that assist in the beneficial processes and common bacteria, which often cause infections. The aim of this article is to analyze the existence of a relationship between the prevalence of pathogenic bacteria and intestinal inflammation when plasma levels are deficient in vitamin D. For this, the literature review was carried out with a systematic search in order to capture the current information. on the topic, in order to contribute to the clinical direction. As a result of the analysis, it was found that vitamin D sufficiency favors the presence of probiotics and intestinal barrier integrity, and that deficiency is associated with the prevalence of pathobionts and intestinal inflammation.*

I. INTRODUCTION

The gut microbiota is established as an organ of the body, influencing local and systemic processes such as nutrition, vitamin supply, maturation of mucosal immunity, and gut-brain communication (Weiss & Hennet, 2017). Thus, it needs an adequate and stable cellular composition, which in this case consists of 30-400 trillion microorganisms, including bacteria (mainly bacteria of the phyla Bacteroidetes, Firmicutes, Actinobacteria and, to a lesser extent, Proteobacteria), fungi and viruses that colonize the human intestine (de Oliveira et al., 2017).

The intestinal tract is sterile at birth, being colonized and shaped by lifelong exposures such as delivery (especially in vaginal delivery, by direct contact with the mother's fecal microbiota), genetic factors, diet, antibiotic use, gestational age and microorganisms from the maternal digestive tract,reaching adult composition at approximately 3 years of age (Yatsunenko et al., 2012). In this sense, alterations in the immune system and in the factors previously exposed can lead to Dysbiosis, a state of imbalance between the number of protective and aggressive bacteria, favoring a metabolic endotoxemia and a chronic inflammatory state, due to the increase in intestinal permeability, which results in an ascending passage. of lipopolysaccharide (LPS) to the systemic circulation (dos Santos Moraes et al., 2017)

Fecal calprotectin, a marker of intestinal inflammation, has been shown to be inversely related to serum vitamin D (VD) concentration in Crohn's disease and Inflammatory Bowel Disease, raising questions about the existence of a bidirectional relationship between vitamin D and inflammation and microbiota. intestinal tract (Naderpoor et al., 2019). Sigh et al., (2020) further described the potential role of vitamin D as a modifier of the gut microbiota in healthy individuals by finding that following VD supplementation there was an increase in the overall diversity of the gut microbiota and, in particular, an

increase in abundance. relative abundance of Bacteroidetes (bacteria related to beneficial effects in the body) and decreased relative abundance of Firmicutes (bacteria often associated with infections).

Vitamin D, despite its name, is considered a steroid hormone that is part of the secosteroid group, derived from 7-dehydrocholesterol (7-DHC), having 1α,25-dihydroxy-vitamin D or calcitriol as an active metabolite; as precursors vitamin D2 or ergosterol, vitamin D3 or cholecalciferol, 25-hydroxyvitamin D [25(OH)D] or calcidiol, and some degradation products. Most vitamin D is synthesized endogenously in the deep layers of the epidermis, as follows: exposure of the skin to ultraviolet rays (UVB) allows the process of photochemical cleavage of the cutaneous precursor of vitamin D, 7-dehydrocholesterol, giving rise to pre-vitamin D3, which undergoes a temperature-dependent molecular rearrangement resulting in the formation of vitamin D3 or cholecalciferol (Marques et al., 2010). Limiting factors for the production of vitamin D are considered to be non-exposure to ultraviolet rays, the use of sunscreens and the degree of skin pigmentation, since black skin has lower penetration of UVB rays (Melmed et al., 2015). A small part can still be obtained through the diet, vitamin D3 (cholecalciferol) is of animal origin and is present in tuna, cod, sardines and salmon; Vitamin D2 (ergosterol) is of plant origin and is also found in edible fungi such as fresh and dried shitake mushrooms (Claudio Gonçalves de Castro, 2011). vitamin D3 (cholecalciferol) is of animal origin and is present in tuna, cod, sardines and salmon; Vitamin D2 (ergosterol) is of plant origin and is also found in edible fungi such as fresh and dried shitake mushrooms (Claudio Gonçalves de Castro, 2011). vitamin D3 (cholecalciferol) is of animal origin and is present in tuna, cod, sardines and salmon; Vitamin D2 (ergosterol) is of plant origin and is also found in edible fungi such as fresh and dried shitake mushrooms (Claudio Gonçalves de Castro, 2011).

In the blood, cholecalciferol and ergosterol are transported to the liver mainly by the vitamin D binding protein, or transcalciferrin, and a small part by albumin, where they are hydroxylated by a cytochrome P450-like enzyme at carbon 25 to form calcidiol (25-OH- Vitamin D) which is the depot form of vitamin D. Finally, calcidiol is transported by DBP to the kidneys where new hydroxylation occurs by the action of the enzyme 1-alpha-hydroxylase, forming calcitriol (1,25-OH-vitamin D), which is the metabolically active form of vitamin D (Científico & De Paula, 2016).

Vitamin D binds to vitamin D receptors (VDRs) and thus can exert its biological functions, as they regulate the transcription of DNA into RNA, similar to other members of the nuclear receptor family. For a long time, the role of vitamin D was solely attributed to the regulation of osteomineral physiology, especially calcium metabolism. However, VDRs are expressed by several cell types, including osteoblasts, osteoclasts, hematopoietic cells, epidermal cells, pancreatic cells, small intestinal epithelium, in addition to being widely expressed in most immune cells, including monocytes, macrophages, dendritic cells. , NK cells and T and B lymphocytes (Marques et al., 2010). The anti-inflammatory effects of vitamin D have been studied extensively in different conditions of subacute, acute, and chronic inflammation, such as obesity, diabetes, and inflammatory bowel disease. In this sense, this study aimed to review the literature in order to gather updated information regarding the relationship between impaired levels of Vitamin D and the consequences of this on intestinal dysbiosis, in order to contribute to clinical guidance.

II. METHODOLOGY

The present study is a systematic literature review, a qualitative-quantitative research (Estrela, 2018; Pereira et al., 2018). For its elaboration, methodological steps were followed in this sequence: (I) elaboration of the research question; (II) search for scientific evidence; (III) selection of articles; (IV) data extraction; (V) assessment of methodological quality; (VI) data synthesis; (VII) assessment of evidence levels; and (VIII) writing and publishing the results.

The search for scientific records was based on the guiding question: “Do low levels of vitamin D favor the development of intestinal dysbiosis?”, formulated using the strategy of the acronym PICO (Population, Intervention, Comparison, Outcome), which in turn time was defined based on the objectives of the present study as:

P: Patients and animals with vitamin

D deficient plasma levels.

I: Vitamin D supplementation.

C: Vitamin D-restricted diet. O: Intestinal dysbiosis.

In order to capture articles that presented in their study designs a correlation between intestinal dysbiosis and vitamin D deficiency. Health Sciences (LILACS), PubMed and Scientific Electronic Library Online (Scielo), using as descriptors the terms “Dysbiosis”, “Vitamin D deficiency” and “Gintestinal microbiome”, identified in the Health Sciences Descriptors (DECS). The research was carried out with descriptors in English on Pubmed and in Portuguese and Spanish on Scielo and LILACS. The search for articles was carried out in each of the databases

following the following steps: initially the search was performed using the three descriptors separately and then, in combination of two and three terms, using the Boolean operator "and". Studies performed in humans and animals, which had good methodological reliability and addressed the relationship between vitamin D and intestinal dysbiosis, were included. The exclusion criteria for the study were articles with a publication time of more than 15 years, articles with incompatible samples, literature reviews and systematic reviews. Thus, 18 articles were found suitable to be addressed, as shown in Figure 1.

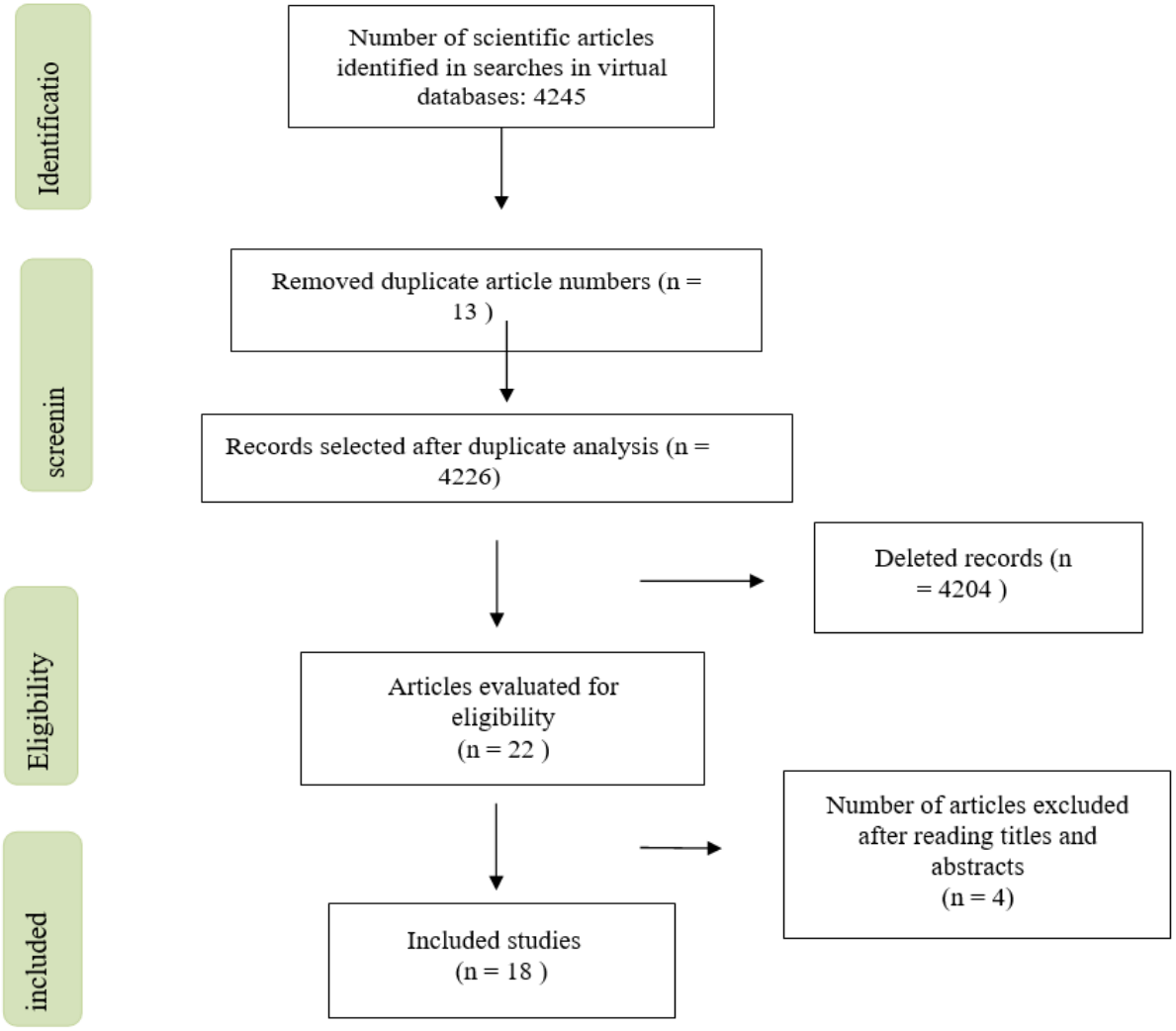

Fig.1. Flowchart of methodological steps for selecting studies.

III. RESULTS AND DISCUSSION

Initially, 4245 articles were obtained: 4234 from PubMed, 5 from Scielo and 6 from Lilacs. After considering the exclusion criteria and analyzing the titles, 22 articles remained from PubMed, 0 from Scielo and 0 from Lilacs: 22 in total, which were selected for full reading of the abstracts. When the abstract proved to be relevant to the research objective, the work was read in full. Finally, 18 texts from PubMed, 0 from Scielo and 0 from Lilacs were selected, reducing the corpus to 18 scientific articles, as shown in Table 1.

The 18 articles were divided as follows: ten studies performed in humans and eight in animals, eight of which were controlled clinical trials, two uncontrolled clinical trials, six randomized and controlled clinical trials, and two in vivo experimental studies, as shown in the Table two.

Table 1.Number of articles per database.

Basis of data	found	selected
PubMe d	4234 articles	18 articles
Scielo	5 articles	no article
lilacs	6 articles	no article

Source: Authors (2021).

Table 2. Distribution of articles according to authors/year of publication, design, level of evidence and main results.

Title of work	Author/Y ear	Outline	Level of evidenc e	main results
1 The effect of vitamin D on intestinal inflammation and fecal microbiota in patients with ulcerative colitis	Garg et al., 2018	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	Vitamin D replacement at a dose of 40,000 IU weekly for 8 weeks reduced markers of intestinal inflammation such as fecal calprotectin in patients with active UC with vitamin D deficiency. This was associated with an increase in Enterobacteriacae, but overall there was no significant changes in the diversity of the microbiota.
two The effect of daily consumption of different doses of fortified Lavash bread versus plain bread on serum vitamin D status, body composition, metabolic and inflammatory biomarkers, and gut microbiota in apparently healthy adults: study protocol of a randomized clinical trial	Tangest ani; Kurosh; Shab- Bidar., 2019	Double- blind, randomize d, controlled clinical trial	Level II - evidence derived from at least one randomiz ed clinical trial	Using bread, a food consumed daily by diverse populations, fortified with vitamin D, in order to improve serum vitamin D levels and determine the effect of vitamin D on body composition, metabolic and inflammatory biomarkers and intestinal microbiota in apparently healthy adults
3 Weekly bolus vitamin D3 supplementation affects gut and airway microbiota in adults with cystic fibrosis: a double-blind, randomized, placebo-controlled clinical trial	Kanher eet al., 2018	Randomiz ed controlled clinical trial	Level II - evidence derived from at least one trial randomiz ed clinical	After 12 weeks, there was a difference in the microbiota of subjects who were randomized to take 50,000 IU of vitamin A once a week. D3 compared to subjects randomized to placebo. The gammaproteobacteria, potentially pathogenic species, were enriched in vitamin D deficiency, in addition to the increase of Bacteroides in the airway microbiota. *Lactococcus*,bacteria associated with Health intestinal tract, were enriched in the presence of vitamin D3.

4 Correlation between vitamin D status and gut microbiota in patients with inflammatory bowel disease	Chen et al., 2020	controlled clinical trial	Level III - clinical trials well outlined , Without randomizati on	There was no difference in the alpha and beta diversity of the microbiota between the sufficient, deficient and insufficient groups of 25(OH)D. However, the abundance of Proteobacteria was higher in the vitamin D deficient group (<30nmol/L) and Actnomycete was higher in the sufficient group of vitamin D (>50nmol/L).
5 Effect of vitamin D supplementation on the fecal microbiota: a randomized clinical trial	Naderp oor et al., 2019	Parallel group, double- blind, randomized , controlled clinical trial	Level II - evidence derived from at least one randomiz ed clinical trial	Participants with a BMI >25kg/m² and no comorbidities received a loading dose of 100,000 international units (IU) of oral cholecalciferol followed by 4000 IU/day (four capsules) for 16 weeks or matching placebo. An increase in abundance was found of Lachnospira and Coprococcus and a decrease in the abundance of Blautia, *Clostridiaceae*and Ruminococcus in individuals with higher serum concentrations of 25(OH)D.
6 Effect and mechanism of vitamin D on colorectal cancer development based on intestinal flora disorder	Zhou et al., 2020	Randomiz ed, controlled clinical trial	Level II - evidence derived from at least one randomiz ed clinical trial	Vitamin D deficiency worsened the deterioration of inflammation and intestinal cancer in mice with colorectal cancer, while the overall condition of the mice improved after vitamin D supplementation (with 1500 or 3000 IU vitamin D3/kg). Vitamin D has a regulatory effect on intestinal probiotics and aids in the integrity of the colonic barrier, which is mediated by Akkermansia muciniphila through the expression of acylglycerols.
7 Vitamin D- restricted high-fat diet downregulates the expression of intestinal alkaline phosphatase isozymes in ovariectomized rats	nakaoka et al., 2018	Experiment al in vivo, controlled and non-randomized	Level III – well- designed clinical trials, without randomiza tion	Vitamin D-restricted high-fat diet down-regulated mRNA expressions ofisozymesIntestinal alkaline phosphatase (IAP) in the duodenum of menopausal animal models. IAP controls bacterial endotoxin-induced inflammation by dephosphorylating thelipopolysaccharide, beinga defense factor of the intestinal mucosa.
8 Vitamin D deficiency alters the gut microbiome, reducing the production of vitamin B in the gut. The resulting lack of pantothenic acid negatively affects the immune system, producing a "pro- inflammatory" state associated with atherosclerosis and autoimmunity.	Gomin ak, 2016	Uncontroll ed clinical trial	Level III – well- designed clinical trials, without randomiza tion	Participants with neurological complaints, sleep problems and symptoms of irritable bowel syndrome (IBS) after supplementation with minimum recommended doses of the 8 B vitamins for three months, plus individual doses of vitamin D in order to maintain blood levels of 60- 80ng/ml on an ongoing basis, most achieved complete resolution of all IBS symptoms by the end of three months. Vitamin D supplementation was maintained and doses of B vitamins were withdrawn. There was also improvement in some sleep and pain complaints.

9 Vitamin D administration leads to a change in intestinal bacterial composition in patients with Crohn's disease, but not in healthy controls.	Shaffler et al., 2018	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	After administration of 20,000IU cholecalciferol for 4 weeks every other day, patients with Chron's Disease had high abundance of some species such as Alistipes, Barnesiella, Roseburia, Anaerotruncus, Subdoligranulum and a Ruminococaceae. Although microbial communities changed significantly, a further increase in vitamin D level was associated with a reversal of this effect, causing a decrease in bacterial richness. However, there were no changes in healthy control patients.
10 The potential role of vitamin D supplementatio n as a gut microbiota modifier in healthy individuals	Singh, 2020	Uncontroll ed clinical trial	Level III – well-designed clinical trials, without randomizati on	Vitamin D supplementation increased the overall diversity of the gut microbiota and, in particular, increased the relative abundance of Bacteroidetes and decreased the relative abundance of Firmicutes. There was also an increase in *phyla Verrucomicrobia*and Actinobacteria. In this sense, it also favored an enterotype dominated by Bacteroides over Prevotella, the latter being considered an intestinal pathobiont.
11 Vitamin D signaling through the induction of panetitic cell defensins maintains the gut microbiota and improves metabolic disorders and hepatic steatosis in animal models	Su et al., 2016	Randomiz ed clinical trial	Level II - evidence derived from at least one randomiz ed clinical trial	Mice fed a high-fat diet + vitamin D (HFD) or a control diet without vitamin D (VDD) developed moderate hepatic steatosis. In contrast, HFD + VDD mice developed severe hepatic steatosis. The degree of steatosis was associated with 25-OH deficiency DV3, as well as the degree of systemic inflammation and the integrity of the ileal mucosal lining. There was growth of H. Hepaticus in the vitamin D deficient groups and suppression of A. Muciniphila.
12 Vitamin D regulates the gut microbiome and protects mice from sodium dextran sulfate- induced colitis Vitamin D regulates the gut microbiome and protects mice from dext sodium sulfate-induced colitis	Ooi et al., 2013	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	The data suggest that in the absence of the VDR or the ability to produce 1,25(OH)2D3, dysregulated gut inflammation results in an environment that supports the expansion of bacteria in the phylum Proteobacteria. Expanding phylum Proteobacteria (including members of the Helicobacteraceae family) competes with beneficial members of phyla Firmicutes and Deferribacters. In this way, epithelial integrity is impaired, dysbiosis, increased inflammation and more severe experimental colitis occur.

13 Impact of vitamin D deficit on the rat intestinal microbiome Impact of vitamin D deficit on the rat intestinal microbiome	Robles- Vera et al., 2019	Randomiz ed, controlled clinical trial	Level II - evidence derived from at least one randomiz ed clinical trial	The animals were allocated into two groups, one with a standard diet plus 1,500 IU/kg of cholecalciferol and one with a personalized diet free of vitamin D, for seven weeks. there was an increase in the Enterobacteriaceae family with significant increases in their genera associated Escherichia , Candidatus blochmannia and Enterobacter , an increase in Prevotellaceae and its genus Prevotella and a decrease in the family Odoribacteraceae and its genus Butyricimonas in the vitamin D free group. α and β diversity.
14 Vitamin D deficiency predisposes to barrier dysfunction induced by adherent invasive Escherichia coli and experimental colonic injury	Assa et al., 2015	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	1,25(OH)2D3 attenuated paracellular permeability induced by adherent invasive Escherichia coli infection and redistribution of junction proteins. Vitamin D deficiency predisposes to changes in barrier function, thus creating an environment that promotes colonization of intestinal tract pathogens and subsequent exacerbation of the inflammatory response.
15 Lack of vitamin D receptor causes dysbiosis and alters murine gut microbiome functions	Jin et al., 2015	In vivo experiment al study	Level III – well- designed clinical trials, without randomiza tion	At the taxonomic level, the Lactobacillales-a-Lactobacillus lineage was dwarfed in fecal samples from Vdr $^{-/-}$. In Vdr -/- mice, Lactobacillus was depleted in feces compared to cecal feces, while Tannerella, *odoribacter*, they are enriched.
16 New role of the receiverof vitamin D in maintenance of barrier integrity of the intestinal mucosa	Kong et al., 2008	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	Mice that had VDR (VDR +/+) were resistant to induced colitis, while those that did not (VDR -/-) developed severe diarrhea, rectal bleeding, body weight loss, and death after 2 weeks. The study found severe damage to the gut epithelial junctions in mice that lacked VDR expression.
17 Impaired 25-hydroxylation of vitamin D in liver injury suppresses intestinal Paneth cell defensins, leading to intestinal dysbiosis and hepatic fibrogenesis	Wu et al., 2020	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	Liver damage and fibrosis are associated with vitamin D (VD) deficiency due to decreased hepatic 25-hydroxylation of VD in the liver. Insufficiency of RV signaling can impair innate intestinal immunity and integrity, including downregulation of Paneth cell functions, leading to increased bacterial translocation to endotoxemia and intestinal dysbiosis, which can consequently promote hepatic fibrogenesis. The increase in intestinal permeability in liver injury and fibrosis was improved by repeated administration of DEFA5, which consequently also reduced plasma endotoxin. Bacteriodetes at the phylum level were decreased in mice with liver damage.

18 Vitamin D deficiency promotes epithelial barrier dysfunction and intestinal inflammation	Assa et al., 2014	controlled clinical trial	Level III – well- designed clinical trials, without randomiza tion	Mice were divided into 4 groups, two infected by C. Rodentium (one group deficient and the other sufficient in vitamin D) and two uninfected (one deficient and the other efficient in vitamin D). *THE*C. rodentium infection in animals increased intestinal permeability and crypt hyperplasia in the vitamin D sufficient group, however, the increase was significantly greater in the vitamin D deficient group. Vitamin D deficiency resulted in higher levels of pro- inflammatory and anti-inflammatory cytokines in both vitamin D-deficient study groups (without and with infection) compared with animals with sufficient vitamin D. In the group of mice infected with vitamin D deficiency, there was an increase in the abundance of Actinobacteria and Gammaproteobacteria.

Source: Authors (2021).

3.1 Influence of vitamin D on the composition of the gastrointestinal microbiota

All records analyzed showed an increase in phyla, families, genera or species of beneficial/probiotic bacteria and a decrease in pathogenic bacteria in cases of vitamin D supplementation, or the reverse, in cases of deficient levels of vitamin D or changes in the receptor of vitamin D (VDR), as in the study by Kanhere et al. (2018), where after patients were supplemented with 50,000 IU of vitamin D3 for 12 weeks, there was an enrichment of Lactococcus, bacteria associated with intestinal health, corroborating reports of a study carried out by Jin et al. (2015), who showed a decrease in Lactobacillus in fecal samples from mice lacking vitamin D receptor (Vdr - / -).

In addition, 95% of the records chosen to compose the present review, which analyzed microbial diversity, did not report significant changes in it, as in the study by Robles-Vera et al. (2019), who found that a diet free of vitamin D for seven weeks did not significantly alter microbial diversity and richness when compared to a standard diet. However, he reported that there was an increase in the Enterobacteriaceae family and its genera Escherichia, Enterobacter , and Candidatus blochmannia species, which are part of the Gammaproteobacteria class and often cause infections in the gastrointestinal, urinary and respiratory tracts; in addition to the opportunistic bacterium Prevotella, often found in infections. Likewise, Naderpoor et al. In addition to favoring an enterotype dominated by Bacteroides over Prevotella, the latter being considered an intestinal pathobiont (Singh et al., 2020). Thus, regardless of the microbial diversity percentile, both studies indicate that vitamin D deficiency may favor an appropriate environment for the establishment of opportunistic pathogens, which cause dysfunctions in the intestinal barrier, promoting bacterial translocation of the pathogen, infection and systemic inflammation.

3.2 Vitamin D levels and impacts on intestinal inflammation

In the present review, 50% of the articles obtained results about the effects of vitamin D or its deficiency on intestinal inflammation. Overall, vitamin D deficient groups (generally levels <30nmol/L) had higher levels of pro-inflammatory and anti-inflammatory cytokines when compared to vitamin D sufficient groups (generally levels >50nmol/L). Like Zhou et al. (2020), where vitamin D deficiency in mice with colorectal cancer increased the deterioration of cancer-caused inflammation, compared with the control group. However, the general condition of the mice improved after vitamin D supplementation (with 1500 or 3000 IU vitamin D3/kg). Similar to the study by Su et al. (2016), who associated worse degrees of steatosis with plasma 25-OH VD3 deficiency, as well as the degree of systemic inflammation and the integrity of the ileal mucosal lining. Furthermore, growth of H. hepaticus was observed in vitamin D deficient groups and suppression of Akkermansia muciniphila. According to the analyses, vitamin D has a regulatory effect on intestinal probiotics, such as Akkermansia muciniphila, a bacterium that improves intestinal permeability by increasing the thickness of the mucus layer of the intestinal mucosa, helping to maintain the integrity of the colonic barrier. Therefore, when suppressed, epithelial integrity is

impaired. Vitamin D has a regulatory effect on intestinal probiotics, such as Akkermansia muciniphila, a bacterium that improves intestinal permeability by increasing the thickness of the mucus layer of the intestinal mucosa, helping to maintain the integrity of the colonic barrier. Therefore, when suppressed, epithelial integrity is impaired. Vitamin D has a regulatory effect on intestinal probiotics, such as Akkermansia muciniphila, a bacterium that improves intestinal permeability by increasing the thickness of the mucus layer of the intestinal mucosa, helping to maintain the integrity of the colonic barrier. Therefore, when suppressed, epithelial integrity is impaired.

Nakaoka et al. (2018) described a different mechanism when finding that a high-fat diet with vitamin D restriction down-regulated the mRNA expressions ofisozymesIntestinal alkaline phosphatase (IAP) in the duodenum of menopausal animal models. IAP controls bacterial endotoxin-induced inflammation by dephosphorylating thelipopolysaccharide, beinga defense factor of the intestinal mucosa. Associated with this, according to Ooi et al. (2013) Vitamin D and VDR prevent Th1, Th17 and the production of inflammatory cytokines in the gastrointestinal tract, reducing inflammation in the gut and controlling dysbiosis. In this sense, in the absence or low expression of the VDR or in the deficiency of producing 1,25 (OH) 2 D 3, dysregulated inflammation of the intestine results in an environment that supports the expansion of bacteria in the phylum Proteobacteria. Expanding phylum Proteobacteria (including members of the Helicobacteraceae family) competes with beneficial members of phyla Firmicutes and Deferribacters. As in the study by Chen et al. (2020), where Proteobacteria was higher in the vitamin D deficient group (<30nmol/L). Thus,

3.3 Vitamin D supplementation as an intestinal protective factor

Kong et al. (2008) when using in vitro culture systems obtained an increase in the levels of tight junction proteins ZO-1, claudin-1, claudin-2 and adherent binding protein E-cadherin after 24 hours of treatment with 1,25(OH) 2 D3. In the study by Ooi et al. (2013), mice that failed to produce 1,25(OH)D (Cyp KO) had substantially less E-cadherin expression than control mice. The analyzed data suggest that vitamin D and VDR may participate in the preservation and integrity of the intestinal barrier by increasing the level of key proteins for the tight junction of the intestine.

The lack of vitamin D receptors altered the function of intestinal epithelial cells (Paneth cells), reducing the production of defensins and lysozyme, antimicrobials that cause changes in the cell wall of pathogenic bacteria, producing their lysis. Thus, VDR defects can impair the immunity and innate integrity of the intestinal barrier, favoring the inflammatory effects and modifications of the intestinal microbiota (Wu et al., 2020). However, 1,25(OH)2D3 supplementation attenuated the paracellular permeability induced by adherent invasive Escherichia coli infection and redistribution of junction proteins (Assa et al., 2015). Similar to the study by Garg et al. (2018), where vitamin D replacement at a dose of 40,000 IU weekly for 8 weeks reduced markers of intestinal inflammation,

IV. CONCLUSION

Based on the analysis of the manuscripts that composed this systematic review, the data report that sufficient levels of vitamin D favor the presence of beneficial bacteria/probiotics (e.g. Lactobacillus, Croococcus, Bacteroidetes and Akkermansia muciniphila) and insufficient levels are associated with the establishment of pathobionts in the intestinal environment (eg, Prevotella, Escherichia, Candidatus blochmannia and Enterobacter). In addition, a trend towards elevated levels of inflammatory cytokines and decreased intestinal permeability in vitamin D deficient levels was demonstrated. However, patients who supplemented with vitamin D had improved intestinal barrier integrity, decreased inflammatory markers, and resolution of intestinal symptoms. Therefore, given the available data, maintaining sufficient serum levels of vitamin D (>50nmol/L) favors intestinal health, enabling an enterotype dominated by probiotics, decreasing inflammatory markers, protecting the integrity of the intestinal barrier, and preventing and treating intestinal and systemic inflammation. However, this review found that not only the presence or deficiency of vitamin D interfered with the results obtained, but also its metabolism; availability; previous infections and pathologies; presence, expression and signaling of the VDR. For a better definition of supplementation doses and adequate plasma levels of vitamin D, greater investments are needed in randomized clinical studies in humans, with standardization of doses and periodicity.

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