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MAJOR CONSIDERATIONS AND OUTCOMES OF CLINICAL STUDIES ON VITAMIN D DEFICIENCY IN HUMAN GUT MICROBIOTA: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: There are 2.0 billion overweight and obese people in the world, and Brazil ranks fifth in the world ranking, with an estimated 18.0 million people. The microbiota of the healthy gastrointestinal system presents around 800 species of bacteria The human microbiome has about 3 million genes in the gastrointestinal tract, corresponding to 150 times more than the human genome Vitamin D appears to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer cells. In addition, there is evidence that vitamin D interferes in vivo and in vitro production of cytokines. The vitamin D plays a significant role in modulating the immune system in the intestine, it is possible that its deficiency could impair the function of the intestinal barrier favoring the translocation of endotoxins such as lipopolysaccharides (LPS) into blood circulation. **Objective:** The present study aimed to investigate the main correlations and outcomes of clinical studies on vitamin D and gut microbiota. **Methodology:** Following the criteria of literary search with the use of the MeSH Terms that were mentioned in the item below on "Search strategies", a total of 55 clinical studies were recruited that were submitted to the eligibility analysis and, after that, 27 studies were selected. The search strategy was performed in the PubMed, Embase, Ovid and Cochrane Library, Web of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier) and OneFile (Gale) databases. **Final considerations:** In summary, there is a modulatory effect of vitamin D status on the intestinal immune system could influence the commensal bacterial composition and vice versa. The relatively greater abundance of gram-negative genera, such as Haemophilus and Veillonella, may be facilitated by low intake and/or concentration of vitamin D. Relatively small proportion of beneficial bacteria, such as Coprococcus and Bifidobacterium, could trigger immune response and inflammation, requiring actions as dependent on 25 (OH) D. It is concluded that vitamin D role in the maintenance of immune homeostasis seems to occur in part by interacting with the intestinal microbiota. Further studies with the appropriate design are desirable to address the hypothesis raised in the present study.

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INTRODUCTION

Obesity represents a multifactorial disease that causes serious public health problems (Luthold, 2017). There are 2.0 billion overweight and obese people in the world (OMS, 2018) and Brazil ranks fifth in the world, with an estimated 18.0 million people, tending to reach 70.0 million individuals (IBGE, 2019).

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The microbiota of the healthy gastrointestinal system presents around 800 species of bacteria, and thousands of these microorganisms live symbiotically with fungi, archaea, and viruses, characterizing each human being with maximum concentration in the colon (Rinninella, 2019). This composition is organized into at least three enterotypes depending on various traits, including genetic background, immune phenotype, eating habits, etc (Arumugam, 2011). In this sense, the human microbiome has about 3 million genes in the gastrointestinal tract, corresponding to 150 times more than the human genome (Huttenhower, 2012). The combination of bacterial cells and genes with host cells and genes leads to the

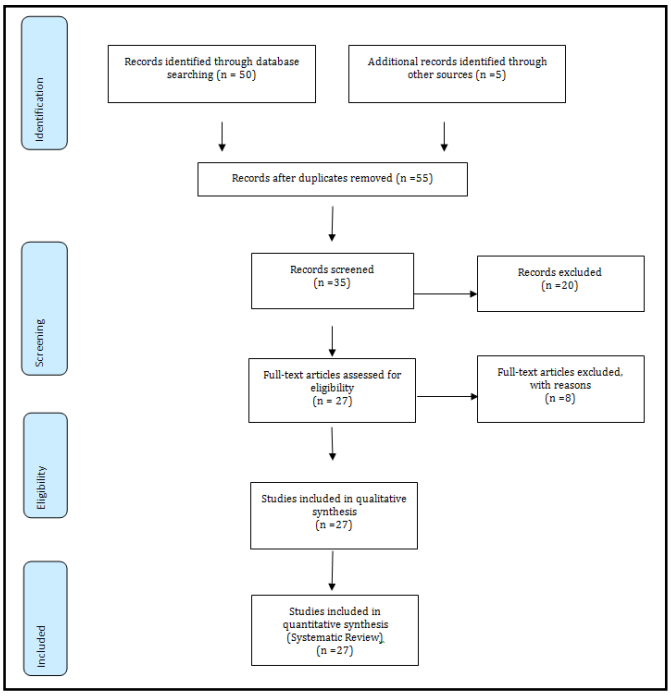
design of a "superorganism." This depends on the appropriate interactions between the intestinal microbiota and the host to achieve and maintain health (De Filippo, 2010). Vitamin D appears to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages and natural killer cells (NK) (Angelakis, 2012). In addition, there is evidence that vitamin D interferes in vivo and in vitro production of cytokines (Wu, 2011). Among the immunomodulatory effects demonstrated to be decreased production of interleukin-2 (IL-2), interferon-gamma (INF-γ) and tumor necrosis factor (TNF), inhibition of IL-6 expression and inhibition of the production and secretion of autoantibodies by B-lymphocytes (Tchernof, 2013). The vitamin D plays a significant role in modulating the immune system in the intestine, it is possible that its deficiency could impair the function of the intestinal barrier favoring the translocation of endotoxins such as lipopolysaccharides (LPS) into the blood circulation (Dewulf, 2013). LPS are known to promote low-grade inflammation, which predisposes the patient to insulin resistance. Numerous circulating biomarkers have been used to assess clinical inflammation and for research purposes (Dewulf, 2013 and Everard, 2013). Certain compositions of the gut microbiota (GM) have been associated with systemic inflammation and metabolic disorders. Particularly, gram-negative bacteria, which contain LPS in their outer layer, have been shown to stimulate immune response and to provoke metabolic endotoxemia, while other genera, such as bifidobacteria, reduce endotoxemia (Everard, 2013). Despite being gram-negative, Akkermansiawas found to improve the intestinal barrier function and to induce beneficial metabolic effects (Hemarajata, 2013).

Vitamin D deficiency and the lack of VDR have been associated with intestinal dysbiosis and increased susceptibility to intestinal diseases (Mani, 2013). Few studies have investigated whether vitamin D status contributes to disorders of glucose metabolism by modulating the composition of the GM (Luthold, 2017 and Arumugam, 2011). A better understanding of the underlying mechanisms of cardiometabolic diseases is important in relation to their impact on population mortality rates. Certain compositions of the GM have been associated with systemic inflammation and metabolic disorders. Particularly, gram-negative bacteria, containing LPS in their outer layer, have been shown to stimulate immune response and to provoke metabolic endotoxemia, while other genera, such as Bifidobacteria, reduce endotoxemia (Yun, 2017). Therefore, using a systematic review, the present study aimed to investigate the main correlations and outcomes of clinical studies on vitamin D and gut microbiota.

MATERIALS AND METHODS

Study design: Following the criteria of literary search with the use of the MeSH Terms that were cited in the item below on "Search strategies", a total of 55 clinical studies were recruited that were submitted to the eligibility analysis and, after that, 27 studies were selected, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http: //www.prisma-statement.org/).

Search Strategy and Information Sources: The search strategy was performed in PubMed, Embase, Ovid and Cochrane Library, Web of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search for MeSH Terms: *Gut microbiota. Vitamin D. Metabolism. Metabolic diseases*, use of boolean "and" between mesh terms and "or" among historical findings. All references are registered in EndNote.



LITERATURE REVIEW AND DISCUSSION

The human gastrointestinal tract (HGIT) is the most densely populated organism with commensal and symbiotic microorganisms, mostly bacteria, but also fungi, archaea and viruses (Luthold, 2017), harboring ten times more bacteria than the number of cells that make up our organism (OMS, 2018). Individuals present distinct bacterial compositions, partly defined genetically and in another determined by individual and environmental characteristics, such as mode of birth (normal delivery or cesarean section), age and eating habits, which results in a great deal of intra and interindividual variability (IBGE, 2019). One of the ways to evaluate the communities living in the HGIT is by the taxonomic classification that distributes the bacteria in phyla, classes, order, family, genus and species (Rinninella, 2019). It is estimated that, in the GM, there are about a thousand species, distributed in more than 50 different phyla. Metagenomic studies indicate that, in the human microbiota, there are about 3.3 million different genes, 150 times more than the human genome (Arumugam, 2011). The GM of each individual is characterized specifically by groups of bacteria called enterotypes (Huttenhower, 2012) Three enterotypes are characterized by three groups of dominant bacteria such as Bacteroides (enterotipo I), Prevotella (enterotipo II), or Ruminococcus (enterotipo III). Each enterotipo harbors different genera of bacteria. These three enterotypes are not just enumerations of bacteria, they are also specifically reassembled by functions. In fact, an enterotype is a harmonious association of several species of bacteria rather than a systematic addition of bacterial species (De Filippo, 2010).

Aproaches On The Vitamin D and Gut Microbiota: The primary source of vitamin D depends on exposure of the skin to sunlight with up to 20.0% coming from ingestion. It is still

controversial as to whether the consumption of foods containing vitamin D has a direct impact on circulating levels (Angelakis, 2007). Vitamin D2 (ergocalciferol) is found in yeast, mushrooms and some vegetables and vitamin D3 (cholecalciferol), synthesized in the skin by ultraviolet radiation, is found in foods of animal origin (Wu, 2011). To be biologically active, vitamin D undergoes hydroxylation in the liver mediated by 25-hydroxylase and in the kidney by 1α-hydroxylase. 1,25-dihydroxyvitamin D is recognized by its specific receptors (VDR) in different cells, primarily in the gut to increase calcium uptake and in the bone to regulate skeletal homeostasis (Tchernof, 2013). Altered metabolic patterns result in metabolic disorders of calcium and phosphorus with vitamin D disorders having been implicated in some diseases (Tchernof, 2013). Vitamin D plays important roles in innate and adaptive immune responses, in the cell cycle and in metabolic processes, evidenced by the reported relationship between its deficiency and the prevalence of immune-mediated disorders, cancer and cardiometabolic diseases (Dewulf, 2013). An inverse correlation between vitamin D concentrations has been described in respect to the prevalence of obesity and type 2 diabetes mellitus (Everard, 2013; Hemarajata, 2013 and Mani, 2013).

VDR play a part in the production of β cells, endothelium, cardiac myocytes and renin suggesting a role for vitamin D in immune-mediated disorders, cancer and cardiometabolic diseases (Hemarajata, 2013; Mani, 2013; Bai, 2017). In addition, there is evidence that vitamin D deficiency increases inflammatory cytokines and reduces insulin sensitivity with both these conditions having been described as pathophysiological links in cardiometabolic diseases (Yun, 2017). Metabolism-induced GMendotoxemia has been associated with increased cardiometabolic risk (Riva, 2017). Vitamin D deficiency could increase the competitive advantage of Haemophilusand Veillonella, as these pathogens are found to be relatively more abundant in subjects with low compared to high intake of vitamin D (Borgo, 2017). These gram-negative bacteria could explain the higher levels of LPS detected in people who ingest low levels of vitamin D (Angelakis, 2018). On the other hand, a relatively small proportion of bacteria with beneficial effects - such as Coprococcus and Bifidobacterium- could activate intestinal immune response and induce local inflammation, requiring anti-inflammatory compensation pathways such as those dependent on 25(OH)D (Belizário, 2018). The Coprococcus and Bifidobacterium maintained inversely associated with 25 (OH) D concentration after adjustments. Both genders were related to adequate homeostasis of BMI and glucose, as well as production of butyrate and anti-inflammatory actions (Tsai, 2019).

It is possible that exposure to a high abundance of those bacteria can attenuate the immune response. Association Coprococcus with vitamin D status was described when the vitamin was supplemented for the treatment of immune-mediated diseases (Luthold, 2017), but not in healthy individuals. In normal participants, the discovery of an association of 25 (OH) D with coprococcus abundance reflects intestinal immune homeostasis and a stable inflammatory systemic state. To the best of our knowledge, no study has shown an association of Bifidobacterium with vitamin D status (Luthold, 2017). The attenuation or abolition of the association of these genera with three different inflammatory markers suggests that inflammation may partially mediate the relationship between vitamin and microbiota concentration. This is in accordance with the reported evidence of its anti-inflammatory action (Tsai, 2019), and with a pro-inflammatory state when vitamin D is lacking (Kayser, 2019). VDR knockout mice exhibited chronic inflammation in the gastrointestinal tract, even in the face of a non-pathogenic microbiota disease. Despite the controversies over a cause-and-effect relationship, there is a consensus that this vitamin is an important mediator of intestinal defenses against infectious diseases agents (Swain Ewald, 2018). Inverse associations between inflammatory markers and 25 (OH) D have been reported. These results support the role of vitamin D in maintaining the homeostasis of the immune system; some authors speculate that this occurs, in part, through interactions with the GM, although the study design excludes establishing cause-and-effect relationships (Vatanen, 2019). It has been previously described that vitamin D deficient rats, exposed to a bacterial pathogen, exhibited increased endotoxin translocation and inflammatory cytokine production. There is a significant inverse correlation of 25(OH)D with E-selectin and C-reactive protein concentrations, suggesting that even among healthy individuals, the vitamin D status may cause an anti-inflammatory condition (Bianchi, 2018). As a matter of fact, several studies have reported that 25(OH)D plays a significant role in the immune system, as low grade inflammation is correlated with higher serum levels as well as higher consumption (Moossavi, 2018). In addition, previous studies show that *Akkermansiamuciniphila*is linked to effects on metabolic and inflammatory profiles (Bell, 2018). Using animal models, *A. muciniphila* benefits intestinal permeability, mucosal layer thickness and the metabolism in obesity and type 2 diabetes (Bell, 2018). Previously, Haemophilus was associated with IBD and with levels of LPS, and Veillonella with increased inflammation cytokines. These gram-negative bacteria have an outer layer of LPS that is less prominent in subgroups of patients with higher intakes of 25(OH)D (Bell, 2018).

Modulation of GutMicrobiota: Microorganisms that colonize the intestine can alter gene expression in intestinal mucosal cells and ultimately alter the function of human gastrointestinal tract (HGIT) (Luthold, 2013). In general, the gutmicrobiota(GM) is mostly composed of non-pathogenic and health-promoting bacteria but, to a small extent, by potentially pathogenic bacteria (Luthold, 2017 and OMS, 2018). The diet is a factor determining the characteristics of intestinal colonization, especially vitamin D. This highly influences long-term host phenotypes and is not abruptly altered by short-term interventions (Rinninella, 2019). There are important gaps in the knowledge about how feeding and other life habits could alter the composition of the microbiota and how the microbiota modulates positively or negatively the energy balance. Some diets can modify the pattern of intestinal colonization from the beginning of life (Rinninella, 2019; Arumugam, 2011). It is suggested that feeding has a direct effect on the GM, which would ultimately result in changes in biochemical reactions in the intestinal lumen (Huttenhower, 2012 and De Filippo, 2010). However, the definition of this effect is still something to be explored, since most of the existing studies present confounding factors and/or low comparability by using different experimental models, such as different methods of analysis, species of animals studied, lack of standardization of the degrees of body adiposity, the age of the participants and the diet employed (Tchernof, 2013).

Furthermore, since vitamin D plays a role in modulating the immune system in the intestine, it is possible that its deficiency could impair the intestinal barrier function favoring the translocation of endotoxins such as lipopolysaccharides (LPS) in the circulation (Luthold, 2017). The LPS are known as low-grade inflammation, which predisposes insulin resistance. Numerous circulating biomarkers have been used to assess clinical inflammation and investigation (OMS, 2018). In this context, many efforts have been made to understand the link between GM composition and obesity, as well as the role of food ingredients, such as pro and prebiotics, in modulating the GM (Everard, 2013). Studies involving the GM composition of obese individuals are still controversial, making it difficult to treat obesity (Hemarajata, 2013).

Conclusion

In summary, there is a modulatory effect of vitamin D status on the intestinal immune system could influence the commensal bacterial composition and vice versa. The relatively greater abundance of gram-negative genera, such as Haemophilus and Veillonella, may be facilitated by low intake and/or concentration of vitamin D. Relatively small proportion of beneficial bacteria, such as Coprococcus and Bifidobacterium, could trigger immune response and inflammation, requiring actions anti-inflammatory as dependent on 25 (OH) D. It is concluded that vitamin D role in maintaining immune homeostasis seems to occur in part by interacting with the intestinal microbiota. Further studies with the appropriate design are desirable to address the hypothesis raised in the present study.

Conflict of interests: There is no conflict of interest between authors.

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