Vitamin D: A New Anti-Asthma Agent? - Literature review

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ABSTRACT
According to Cotran; Kumar and Robbins (2015), the pathophysiology of asthma is characterized by two reactions, immediate and late, but also by the production of interleukin (IL) 4, IL-5 and IL-13 by Th2 lymphocytes, thus IL-4 and IL -13 are responsible for inducing the expression of IgE by B lymphocytes, in addition, IL-13 also acts by increasing the production of mucus in the airways and IL-5 acts on the differentiation and activation of eosinophils. Thus, in the immediate phase, degranulation of mast cells occurs through IgE, with subsequent release of histamine and Leukotrienes (LT) C4 and D4. In the late phase, the recruitment of more inflammatory cells such as Th2 lymphocytes and eosinophils is observed.

Keywords: Pathophysiology, Asthma, Th2 lymphocytes.

1 INTRODUCTION

According to Cotran; Kumar and Robbins (2015), the pathophysiology of asthma is characterized by two reactions, immediate and late, but also by the production of interleukin (IL) 4, IL-5 and IL-13 by Th2 lymphocytes, thus IL-4 and IL -13 are responsible for inducing the expression of IgE by B lymphocytes, in addition, IL-13 also acts by increasing the production of mucus in the airways and IL-5 acts on the differentiation and activation of eosinophils. Thus, in the immediate phase, degranulation of mast cells occurs through IgE, with subsequent release of histamine and Leukotrienes (LT) C4 and D4. In the late phase, the recruitment of more inflammatory cells such as Th2 lymphocytes and eosinophils is observed.

From a clinical point of view, the Global Initiative for Asthma (GINA) proposes that asthma is a respiratory disorder whose symptoms include reversible airflow obstruction, chest tightness, wheezing and dry cough. Furthermore, it reinforces that these symptoms are subject to variations in intensity and frequency, which can be caused by climate changes, physical activity, viral infections and exposure to allergens.

Therefore, asthma treatment consists of blocking inflammatory reactions and preventing exacerbations. (PIZZICHINI et al., 2020) Therefore, glucocorticoids are essential in the pharmacological therapy of the disease, due to the immunosuppressive nature of these drugs (WILLIAMS, 2018), also because they suppress the production of Th2 cytokines and the induction of eosinophil apoptosis. (DUNICAN; FAHY, 2017)

However, corticosteroid therapy is not perfect and presents a series of adverse effects, whether through inhaled (ICS) or systemic corticosteroids. According to Pizzichini et al. (2020) the use of IC can cause oral candidiasis, dysphonia and throat irritation. Prolonged use of systemic corticosteroids leads to even more worrying effects, such as osteoporosis; Cushing's syndrome; weight gain and dyslipidemia; cardiovascular diseases and diabetes. (LIU et al, 2013)

In this line of reasoning, other drugs have been considered as possible adjuvants in the pharmacological treatment of asthma. Among them are statins, phosphodiesterase 5 inhibitors and Vitamin D. In the randomized clinical study by Naing and Ni (2020), atorvastatin was studied as a possible adjuvant in the treatment of asthma. The study brought uncertain spirometric results (pre and post FEV1 and PEF) when comparing atorvastatin and placebo, however this statin showed a reduction in sputum cells and better results in the Asthma Control Questionnaire (ACQ) compared to placebo. Despite the results obtained, the authors pointed out that this is still not enough to recommend the use of statins in the treatment of asthma.

In the article by Borsi et al. (2019), the effectiveness of daily use of Sildenafil 50 mg was investigated in order to improve lung function and quality of life. The study was conducted in Iran, on 20 patients with severe and uncontrolled asthma. In addition to receiving conventional treatment according to the stage of the disease, 10 people were treated with 50 mg of sildenafil daily and another 10 received a placebo at the same dose. Daily administration of sildenafil did not show major improvements in spirometric values of FEV1, FEV1/FVC, FVC and FEF25-75. Patients were also subjected to a quality of life questionnaire, where the group treated with sildenafil did not show significant improvement compared to the group that received placebo.

Despite its primary action on osteomineral metabolism and calcium and phosphate homeostasis, Vitamin D has been postulated as a possible anti-inflammatory agent. Deficiency of this hormone has been observed in asthma, diabetes and rheumatoid arthritis, being associated with excessive inflammation and imbalance of the immune system. (SASSI; TAMONE; D'AMELIO, 2018) Therefore, the objective of this study is to collect data from the literature on Vitamin D as an adjuvant in the treatment of asthma.

2 GOAL

Asthma is a chronic and inflammatory disease that can lead to irreversible damage, such as airway remodeling. Therefore, a literature review was carried out on the applicability of Vitamin D in the treatment of asthma, with the objective of collecting data related to the action of Vitamin D on cells, interleukins and other characteristic markers of asthma; quality of life of asthmatic patients; prevention of exacerbations and lung function through spirometric values.

3 METHODOLOGY

Data were collected from scientific literature, taken from books and articles published in the last 6 years. However, references that were not published in the proposed period were used as they are essential in the development and contextualization of this review. The articles were taken from digital platforms such as Cochrane Library, Scielo and Pubmed. The keywords used were: Vitamin D; asthma; Th2.

4 DEVELOPMENT

The study by Zhou et al. (2023) tested the benefits of Vitamin D in asthmatic patients through serum levels of interleukins and spirometric results. 136 people were selected to participate in this study, 60 asthmatic patients classified as T2-high (inflammation with significant involvement of Th2 cells, FeNO > 20 ppb and blood eosinophil count > 150 cells/µL), another 30 patients diagnosed with asthma but with a T2-low pattern (inflammation with little involvement of Th2 lymphocytes, presenting more neutrophils, FeNO ≤ 20 ppb and eosinophil count ≤ 150 cells/µL), the other 40 participants were the control. Then, through radioimmunological tests, the serum levels of Vitamin D of asthmatic patients were determined, from this an average was made and the patients were those deficient in Vitamin D (Lo) and those with satisfactory levels of Vitamin D (Hi). In this way, participants underwent the asthma control test (ACT) and it was observed that the scores of patients with Vitamin D deficiency were considerably lower than the scores of patients who had regular levels of this hormone. Furthermore, patients with T2-low asthma who were deficient in vitamin D achieved spirometric values of FVC% and PEF% lower than those of T2-low patients with good levels of vitamin D. An increase in the number of eosinophils in those who were deficient in the Vitamin. IL-5 levels in T2-high (Lo) patients were increased, in the same way that IL-17 levels in T2-low (Lo) patients were also elevated.

The systematic review and meta-analysis study by Wang et al. (2022) brought together the results of several randomized clinical studies on the use of Vitamin D in the treatment of asthma and COPD. It was proposed that Vitamin D supplementation may have effects on FEV1% and the FEV1/FVC ratio, the latter being mainly in asthma. However, no improvement in quality of life or reduction in symptoms was observed in asthmatic individuals. Another study also points to the existence of a favorable relationship between Vitamin D levels and the FEV1/FVC ratio in asthmatic smokers. (TAMAŠAUSKIENĖ et al., 2015)

A cross-sectional study carried out in Minas Gerais from November 2016 to September 2017 associated deficient or insufficient Vitamin D levels with wheezing in pediatric patients. 124 patients with periodic wheezing or asthmatics participated in the study. 25(OH)D levels were determined through immunoassays and then the values corresponding to vitamin D deficiency, insufficiency and sufficiency were, respectively, below 20 ng/mL; 21-29 ng/mL and above 30 ng/mL. Thus, it was observed that in

asthmatic patients who had frequent episodes of wheezing, the prevalence of Vitamin D deficiency and insufficiency was 57.3%. (PEÇANHA et al., 2019)

Amorim et al. (2020) investigated the relationship between Vitamin D and eosinophilic and IgE levels in asthmatic children. In this study, carried out between May and August 2019 in Londrina - PR, the participants included were those with a diagnosis of asthma established by GINA who were undergoing outpatient follow-up; constant use of inhaled corticosteroids; clinical stabilization without exacerbations in the last month. Patients who had recent exacerbations or used medication that could compromise the metabolism of Vitamin D did not participate in the study. Then, participants were divided into two groups, individuals with Vitamin D levels above and below 24 ng/mL. An increase in the number of eosinophils and IgE was observed in the group with Vitamin D levels lower than 24 ng/mL, when compared to the group with good levels of the vitamin.

Regarding the prevention of exacerbations, Williamson et al. (2023) carried out a systematic review and meta-analysis, where they collected data from twenty double-blind randomized placebo-controlled clinical trials of vitamin D supplementation in asthmatic patients. Of these twenty studies, fifteen contributed relevant information to the analysis of the protective effect of Vitamin D in preventing exacerbations. The authors state that there was no effect of vitamin D on the proportion of patients who had one or more exacerbations, and it is almost certain that vitamin D supplementation has a reduction of up to 19% in the chances of one or more exacerbations occurring. One of the studies analyzed pointed out that there is no benefit in the administration of cholecalciferol, however the rate of exacerbations was reduced with the oral use of calcidiol.

The applicability of Vitamin D in the treatment of asthma was also evaluated through experiments in animal models. Feng et al. (2021) in their test sensitized mice with ovalbumin through intraperitoneal injections (20 µg ovalbumin with 50 µL of aluminum hydroxide) and inhalations of 1% aerosolized ovalbumin. The mice were then separated into groups, two of these groups received vitamin D, one took the compound orally and the other took inhalation. During the trial, it was observed that the levels of IL-4, IL-5 and IL-13 as well as IgE and histamine and mucus production significantly decreased in animals that received oral Vitamin D treatment. However, in mice that inhaled Vitamin D, only IL-13 showed a considerable drop, IgE levels were not significantly reduced, histamine was initially greatly reduced, but a few days later this reduction became irrelevant. Other experimental works such as that of Cho et al. (2019) presented similar results. In this trial, through bronchoalveolar lavage of mice that received injections of vitamin D before and after ovalbumin sensitization, a reduction in the levels of IL-4, IL-5 and IgE was evidenced, with the most significant decrease being that of IL- 4.

Ma et al. (2021) demonstrated through animal experimentation that Vitamin D has a protective effect in asthmatic animals (sensitized by ovalbumin). The administration of 50 ng/mL and 100 ng/mL of Vitamin

D was able to significantly reduce serum IgE levels. At the same time, there was an intense restoration of the airways with the use of 100 ng/mL of vitamin D. In addition to these results, the study provided more information regarding the anti-inflammatory properties of Vitamin D, which blocked the NF-κB pathway, resulting in a decrease in the expression of IL-17 and an increase in the levels of anti-inflammatory cytokines IL -10 and TGF-β1.

This time, in the experiment carried out by Huang et al. (2019) it was proposed that Vitamin D reduces airway remodeling through an inhibition of the Wnt/β-catenin signaling pathway. In this study, when comparing the group of asthmatic mice with the group of sensitized mice that received 100 ng/mL of Vitamin D, it was seen that Vitamin D supplementation caused a reduction in the remodeling of the airways, as well as the number of inflammatory cells. present in the lung. Furthermore, this protective effect of the airways was related to an inhibition of the Wnt/β-catenin signaling pathway, as asthmatic mice showed an increase in the expression of Wnt5a mRNA and β-catenin, while in animals treated with Vitamin D this stimulation was inhibited.

Grund et al. (2023) carried out an experiment in an animal model sensitizing mice with ovalbumin and consequently turning them into asthmatic animals. In this way, the mice were divided into two categories, one group received a diet rich in Vitamin D, while the other group was subjected to a diet deficient in Vitamin D. The animals that received the diet rich in Vitamin D presented less resistance to airflow in the airways, which is suggestive that Vitamin D has attenuated airway hyperresponsiveness. When comparing the two groups, an increase in IL-10 secretion and a drop in IgE levels were reported in the group that took Vitamin D supplementation. However, the animals that received the diet low in Vitamin D presented levels of IL-10. 4 lower than those of mice fed a diet rich in Vitamin D.

5 FINAL CONSIDERATIONS

Asthma is a chronic allergic-inflammatory disease of the airways, characterized by acute airflow limitation and bronchial hyperreactivity. Asthma treatment aims to suppress the exacerbated allergic-inflammatory response. In this sense, glucocorticoids, due to their powerful anti-inflammatory actions, are widely used. However, conventional treatment with corticosteroids has limitations and adverse effects. Along this line of reasoning, some research has postulated that “off-label” drugs such as phosphodiesterase 5 inhibitors, statins and Vitamin D can contribute to improving asthma symptoms. Research suggests that Vitamin D deficiency is related to spirometric values in asthmatic patients and levels of interleukins and other typical asthma biomarkers. However, there is still no strong evidence on a possible protective role of Vitamin D, preventing exacerbations and improving quality of life. Therefore, the benefits of vitamin D in the treatment of asthma are still discreet and uncertain, and further studies on the subject are necessary.

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