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Literature Review

# Humoral Immunity in the Context of the Relationship between Periodontitis and Severe Asthma - Literature Review

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## Abstract

Asthma is a chronic disease affecting the airways. Several studies have suggested that some infectious diseases may increase the risk of asthma, such as periodontitis, an inflammatory disease triggered by interactions between the immune system and pathogens present in the subgingival biofilm. The aim of this study was to perform a literature review with respect to the role of the humoral immune response in the context of the relationship between periodontitis and severe asthma. Articles were obtained via PUBMED, MEDLINE and GOOGLE SCHOLAR sites using the following descriptors: asthma, periodontal disease and humoral immunity. The boolean operator "and" was used to combine the descriptors. The search was limited to articles published between 2007 and 2017. Some studies showed a possible association between periodontitis and severe asthma, as the frequency of periodontitis is more elevated among individuals with severe asthma than among those without the diagnosis of this bronchial inflammation. Although the production of Immunoglobulin G (IgG) against periodontal pathogens, such as Porphyromonas gingivalis, has been strongly associated with periodontitis, it remains unclear whether this immunoglobulin plays any role in the association between periodontitis and severe asthma.

***Keywords:*** *Periodontitis; Immunoglobulin G; Asthma; Periodontal Infection; Humoral Immune Response*

## Abbreviations

IgG: Immunoglobulin G; IL: Interleukin; IgE: Immunoglobulin E; ILC2: Type 2 Innate Lymphoid Cells; TLR: Toll-Like Receptors; Treg: T Regulatory Cells

## Introduction

Severe asthma is a respiratory disease characterized by an increase of bronchial inflammation, reversible airflow limitation with frequent episodes of short and gasping breath [1]. The prevalence of asthma in all age ranges, gender and racial groups has been increased since 1980s [2] and the world health organization (WHO) estimates that 334 million of people suffer of asthma worldwide, being more common in children [2].

Asthma is considered a public health problem in a variety of countries, regardless the level of development. When untreated, directly impact the life quality of affected individuals. More than 80% of asthma deaths occurs in countries with low or middle-low incomes [3].

Some aspects of the etiology of asthma, especially severe asthma, are not completely understood. It is known that a combination of genetic predisposition with an exposure to inhaled and particulates can provoke allergic reactions and or airways irritation [2,4]. In addition to this combination, infectious diseases caused by *Chlamydophila pneumoniae* [5], *Mycoplasma pneumoniae* [6], *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* [7] can be associated to the risk of asthma.

In this context, periodontitis seems to be related to asthma, particularly to the severe level of the disease [1,8,9]. A previous study reported that periodontitis can influence the development of severe asthma, since individuals with this periodontal disease showed five-fold chance of having the bronchial inflammation, when compared to individuals without periodontitis [8,9]. However, the biological plausibility of this association remains unclear.

Since the pathogenesis of periodontitis is related to high levels of Immunoglobulin G (IgG) directed to periodontal pathogens in affected individuals [10,11], the aim of the present study was to review the literature on the role of the humoral immunity, specially the production of IgG, in the context of the relationship between periodontitis and asthma.

## Method

A narrative review of the literature on the role of IgG anti-*Porphyromonas gingivalis* in severe asthma was performed. The database PUBMED, MEDLINE and Google Scholar were used to the search of article published from 2007 to 2017. A search in the Scielo database was undertaken, but it was not found any study related to the theme. The descriptors were selected using the Medical Subjects Heading (MeSH). After the selection, the search was realized using the descriptors asthma, periodontal disease, humoral immunity, only in the English language, and the Boolean operator "and" was used to combine the descriptors.

The articles which did not present in the abstract the approach cited above, or were repeated in the databases, were excluded, as shown in the figure 1.

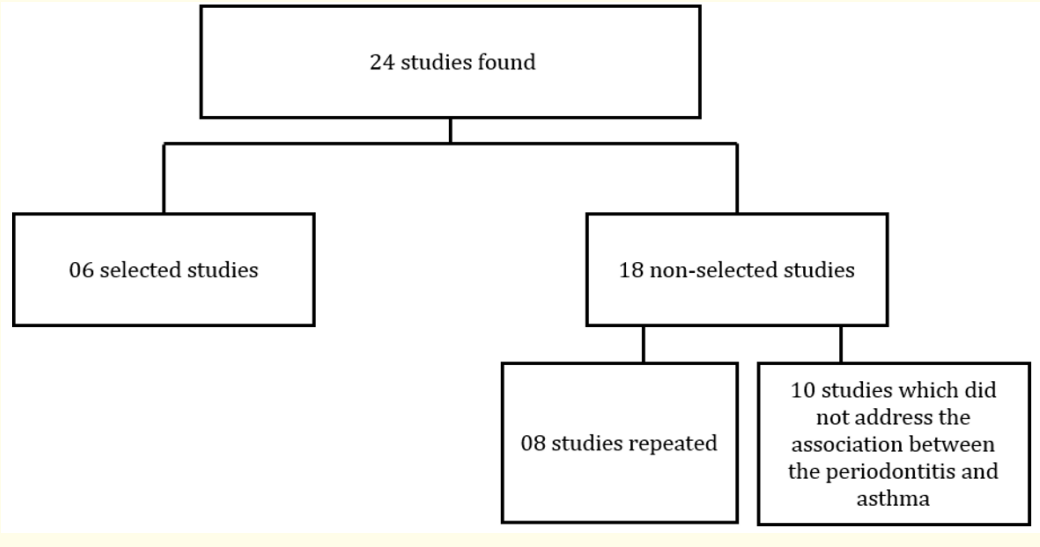


***Figure 1:*** *Flowchart with the result of the search.*

## Literature Review

### Asthma and immune response

Innate and adaptive immune cells are involved in the pathogenesis of asthma. Such cells act concomitantly with the epithelial initiating bronchial hyperactivity, overproduction of mucus and remodeling and narrowing of the airways wall [12].

Atopic asthma is characterized by the presence of an eosinophilic infiltrate [13] detected in spits, as well as in mucosal biopsies, due to the increase in the amount of TCD4+ cells, which secret interleukin (IL)-4 and IL-5 [14].

Although asthma is associated with eosinophilia and the presence of cytokines of the Th2 profile, some asthmatic non-atopic individuals show a predominance of neutrophils and absence of this mentioned profile. Individuals suffering from severe asthma seems to have a neutrophilic inflammation, with a less reversible airways obstruction and the shift to Th1 and Th17 cytokine profiles [15].

Initially, allergens trigger the asthmatic process, activating the immunoglobulin E (IgE) present on the surface of the mastocytes and basophils. These cells express receptors with high affinity to IgE (FcεRI) in the membrane [16]. Such structures are observed in bronchial biopsies derived from asthmatic subjects, regardless the atopy condition [17].

In the atopic asthma, after the above mentioned activation, IL-5, IL-13 and IL-4 are produced [18], arising the clinical signs of the disease. The Th17 profile is also elicited, and IL-17 can have a protector role or can exacerbate the disease, depending on its stadium [19]. The role of the Th17 profile in the atopic asthma remains unclear.

In addition to the Th2 immune cells, the innate lymphoid cells are activated in response to the action of the IL-4 and the transcription factor GATA-3 [20]. The activated Th2 lymphocytes and type 2 innate lymphoid cells (ILC2) secrete IL-5 and IL-13, and, consequently, occur the clinical manifestation of the disease [21].

In murine model, asthma can also be regulated by the complement system molecule C5a. After coupling with its receptor, C5aR, C5a recruits a variety of cells that produces IL-4, IL-5, IL-13, IL-9 and other inflammatory mediators, leading to the onset of the symptoms. In contrast, it is suggested that the production of IgG1 and IgG4 specific to allergens can decrease the immunological inflammation in asthma [22].

With regard to the humoral immune response, the participation of IgE in the pathogenesis of asthma is very well understood [23]. Nevertheless, the literature related to the role of the IgG in this disease is scarce, although some studies have demonstrated its involvement in the physiopathology of asthma [24,25].

### Periodontitis and immune response

Periodontitis is an inflammatory disease resulting of an unbalance in the interaction between periodontopathogens in the subgingival biofilm and the host inflammatory and immune response [26]. In addition to gingival inflammation, this disease affects the periodontal support tissues [27], causing alveolar bone resorption, clinical attachment loss and periodontal pocket formation [27].

The etiology of periodontitis is multifactorial, resulting of the interaction among microbial factors, host genetic and immunological aspects and environmental modulators [28]. The presence of Gram-negative bacteria, such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia* and *Treponema denticola*, can trigger the immune response [26].

The recognition of the microorganisms by toll-like receptors (TLR) expressed on the surface of the resident cells and lymphocytes, particularly TLR 2, 3, 4 and 9, indicates the innate immune response in the pathogenesis of periodontitis [29]. With regard to the adaptive response, it is known that the T $CD4^+$ cells plays a crucial role, but the literature is not consensual about the cytokine profile elicited (Th1, Th2, Th17 or Treg) [29,30].

The Th1 lymphocytes express the transcription factor T-bet and secrete the cytokines IL-2, IFN-γ and TNF [31]. Such cytokines stimulates the osteoclast maturation, leading to the bone loss [32,33]. Other phenotype involved in periodontitis is Th17 CD4+ cells. This profile is induced by a complex cytokine network, including TGFβ, IL-6, IL-21 and IL-23 and involving the transcription factor ROR-ϒT [34]. The cytokines produced after the Th17 cells activation are secreted in periodontal lesions and can contribute to the progression of the disease [32,35].

The Th17 cells can act alone or together with the Th1 cells, since both profile are characterized by recruitment of macrophages and neutrophils and proinflammatory activities [35] that contributes to the exacerbation oh the host response in the affected periodontal tissues.

The participation of the T regulatory (Treg) cells has been reported. These seems to protect against the periodontal tissue destruction [36]. The cytokines associated with Treg cells, such as IL-10 and TGF-β, participate of the tissue repair in the periodontitis [37].

Moreover, it has been reported the role of Th2 lymphocytes, which are dependent of IL-4 and GATA3 to be activated [38,39]. IL-4 inhibit the transcription of Th1 cytokines, such as IFN-γ, matrix metalloproteinases and osteoclastogenic factor RANKL [38,40,41], playing, therefore, a protector role in the periodontal diseases [42] similar and complementary to IL-10 [43].

In addition to the involvement of T cells in the response against Gram-negative microorganisms, the participation of B cells and plasma cells have been reported. High amounts of these cells are present in the tissues with periodontitis, mainly in late stages [44]. They secret IgG specific to periodontal pathogens and express RANKL [44], participating on the induction of the pathological bone resorption in periodontitis [44]. Specific antibodies against periodontal pathogens seems unable to interrupt the progression of the disease, which suggest that they cannot reach an effective antibacterial blocking.

The production of antibodies reactive to *Porphyromonas gingivalis* by individuals with periodontitis has been demonstrated [8,45,46]. Diseased individuals showed higher serum levels of IgG against the extract of *Porphyromonas gingivalis* ATCC33277 compared to those with gingivitis or clinically healthy [10,46]. However, there is a diversity in the serum response pattern of individuals with periodontitis: some of them present an exacerbated immunoreactivity, while others demonstrate low reactivity, although its levels are above the reference values stablished in the test [10].

*Porphyromonas gingivalis* can use a variety of virulence factors and evade the host defense, deregulating the inflammatory and immune responses [47]. One of these components is the lipoprotein HmuY, a heme ligand associated with the outer membrane of the bacterial cell [48,49], whose expression is increased when the availability of iron/heme is low in the microenvironment [49].

HmuY is recognized by the immune system in periodontitis, and the production of antibodies directed to this protein can inhibit the biofilm formation [48]. Individuals with chronic periodontitis present high levels of anti-HmuY IgG and IgG1, demonstrating the immunogenic potential of the protein. Furthermore, the HmuY is able to elicit an inflammatory process by inducing the proinflammatory cytokines production [50].

In this perspective, it has been suggested that the understanding of the humoral immune response can collaborate to classify the distinct states of periodontal disease [10] and to the knowledge of the biological plausibility of the association between the periodontitis and other diseases, such as asthma.

## The role of IgG anti-*Porphyromonas gingivalis* in the asthma

The association between periodontitis and asthma has been reported by previous studies [7,51], considering the inflammatory aspects of these diseases. In individuals with severe asthma, the control of the symptoms can be reached with high doses of corticosteroids. Some patients need to receive supplementary doses of oral corticosteroids to the disease control [2]. Thus, the harmful effect of the corticosteroids on the bone mass is more intense during the six first months of usage, which can contribute to the induction of the periodontal destruction.

These corticosteroids act in the periodontal tissues directly influencing the epithelial lymphocytes and macrophages, decreasing the synthesis of collagen, causing damages in the bone metabolism, in addition to reduce the number of activated lymphocytes and the influx of phagocytes [52]. The systemic bone loss induced by these drugs, mainly in patients who use high doses during long periods of time, can exert an important role in the development and progression of periodontitis [1].

On the other hand, the current knowledge on the immune response against oral bacteria and the pathogenesis of the periodontal diseases has suggested the involvement of biological mechanisms by which oral pathogens can influence respiratory diseases, such as pneumonia and asthma, through the sensitization of the epithelium caused by the stablished inflammatory process. In this process, immunological and inflammatory mediators, such as cytokines and metalloproteinases, can act local and systemically, exacerbating the symptoms of the periodontal and bronchial diseases [53-55].

Previous studies have demonstrated an increase in the concentration of IgE in the gingival tissue, but the participation of this immunoglobulin in the establishment of the periodontal destruction has not been proved to date. This elevated concentration is also found in more severe gingival inflammation conditions in individuals without asthma, despite the immune defense mechanisms are not altered [56]. Thus, the hypersensitivity reactions of the asthma can be related to the development of the periodontitis, since the IgE levels are increased in the gingival tissue [57].

With regard with the IgG, high levels of this immunoglobulin specific to *Porphyromonas gingivalis* were significantly associated with lower prevalence of asthma, wheezing and allergic rhinitis, while high levels of IgG specific to *Aggregatibacter actinomycetemcomitans* were associated with low prevalence of wheezing. Thus, the colonization of the oral cavity by pathogens can exert a protector role in the etiology of the allergic disease [58].

As aforementioned, the literature widely demonstrate the involvement of IgE in the atopic asthma [18] but the same is not observed in relation to the role of IgE in the immunopathogenesis of the periodontal diseases, with IgG being the most reported immunoglobulin [10,45,50,58-60]. Even so, the production of immunoglobulins against periodontal pathogens can explain, at least in part, the relationship between these two diseases. Thus, the study of IgG specific to periodontal pathogens, such as *Porphyromonas gingivalis,* can be an attempt to determine whether it can be a biological marker to predict the worsening of asthma symptoms.

## Conclusion

Studies that address the involvement of biological molecules in the association between periodontitis and asthma are scarce. Of the six articles selected after the literature search, only one evaluated humoral immune response specific to *Porphyromonas gingivalis* in asthma, finding an inverse relationship between the IgG production and the symptoms of the respiratory disease. It is possible that the local immune response induced by this pathogen negatively contribute to modulate the systemic response in individuals with respiratory diseases.

Moreover, it is important to emphasize that this is a two-way relationship. Thus, it is possible that asthma exert an influence in the pathogenesis of periodontitis, altering the production of IgG specific to the periodontal bacteria, since the atopic background of the patients with asthma determine an increase in the IgE serum levels and can also modulate the IgG production.

In view of the above, additional studies are needed to investigate the role of immunoglobulins in the association between periodontitis and asthma, taking in account other conditions that can influence this association.

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## Conflict of Interest

The authors report no conflicts of interest related to this study.

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