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Association between Asthma and Periodontitis: A Literature Review

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Abstract

Both asthma and periodontitis are multifactorial and highly prevalent with global burden chronic diseases sharing similar genetic, environmental, infectious, and inflammatory factors. The first attempts to study the relationship between asthma and periodontal diseases started in the 1970s and continued till now a days. However, to this date no direct causality had been proven between periodontal diseases and asthma, but a strong body of evidence supports a positive association between them. Although many studies found a positive association between asthma and periodontitis, while on the opposite direction many studies did find an inverse type of relationship, and some studies did not find any sort of association which referred to the diverging finding in the literature regarding asthma and periodontitis, these conflicting results may be attributed to the shared risk factors and to the lack of standardizations in defining periodontal diseases and asthma leading to inconsistent results in different studies. We did this literature review to systematically revisit the current evidence concerning the complicated and often conflicting researches studying the link between asthma and periodontitis trying to have better understanding of this complex relationship.

Keywords: Periodontal inflammation, Oral systemic link, Periodontitis, Asthma, Periodontal pathogens, Immune-inflammatory pathway, Chronic diseases

Introduction

Both asthma and periodontitis are widely distributed chronic diseases sharing similar path for initiation and development of the disease process, in reviewing the literature regarding association between periodontitis and asthma, there is conflicting evidence as many studies showed positive association while some studies did not find any type of association and others did find an inverse relation represented in decreased asthma cases in severe periodontitis. We performed this literature review to revise researches studying the association between asthma and periodontitis

Asthma

Asthma is a critical world-wide health dilemma and one of the commonest non communicable diseases (NCDs) that is defined by the global initiative for asthma as "a heterogeneous disease defined by the history of respiratory symptoms (*e.g.* wheeze, shortness of breath, chest tightness, and cough) that vary over time and in intensity, together with variable expiratory airflow limitation". This airflow limitation may later have repeated pattern. Asthma is usually associated with hyper-responsiveness of the airway and continuous inflammation [1].

Two of the five interventions endorsed by World Health Organization to tackle NCDs, smoking control, and primary medicament and technologies will directly reduce the global burden of asthma. A third intervention with the aim of lowering obesity, that is healthy food and physical activity is likely to be advantageous for asthma [2].

In 2019, the Global Burden of Disease Study (GBD) speculated that more than 262 million people had asthma with a rate of 3,416 asthma cases per every 100,000, and in the same statement, deaths from asthma have been shown to be 461,000 with more than 1,000 deaths every day [3].

Asthma is a disease entity that differs in terms of severity, therapy response, initial presentation, symptoms and triggers. Some clinicians think of asthma as single disease that appears in different presentations, others think that different patterns of asthma are separate cases that share common symptoms [3].

The way the clinicians used to look at asthma is that of increased T-helper cell type 2 (Th2) cell responses and allergy-related IgE causing airway hyper-responsiveness. While this accurately communicates the predominant mechanisms of allergic asthma, however asthma is now considered an "umbrella diagnosis with distinct visible properties (phenotypes) and mechanisms (endotypes) all of which manifest with symptoms of wheezing and shortness of breath to cough and chest tightness, and are accompanied by variable airflow obstruction" [4,5].

Two essential types of fundamental asthma medications are present: short-acting bronchodilator inhalers or what be called short-acting β_2-agonist (SABA) reliever which give only short–term symptoms relief and inhaled corticosteroid (ICS)-containing therapies, which treat the possible causative airway inflammation. Unfortunately, many patients with asthma are being managed without ICS, as shown by the new Global Asthma Network (GAN) study [2].

For many years, the most basic treatment step, recommended in most guidelines for the milder or intermittent cases of asthma, has been a short-acting β_2-agonist reliever, which relieves bronchoconstriction quickly and efficiently but does not reduce or treat the underlying inflammatory process usually occurring even in mild asthma, SABA recommendation to be used alone as a first line treatment for mild asthma goes back to a period when asthma was thought to be a disease that composed of only bronchoconstriction. Over-dependence on β_2-agonist bronchodilators may even make the inflammation worse and increase the risk of acute exacerbations and hospital admissions [6].

In their 2019 Strategy, the Global Initiative for Asthma (GINA) made a historic and important shift in the recommendations for controlling asthma. This resulted from a comprehensive revision of evidence on the adverse events of SABA-only treatment and the effect of ICS on asthma acute exacerbations as well as mortality rate in mild asthmatic patients [1].

In the current new recommendations, the use of as-needed ICS in combination with formoterol (a long-acting β2-agonist with quick onset of action) was suggested and in comparison, with as-needed SABA alone, as-needed ICS-formoterol in adults and children ≥12 years with milder asthma decreased exacerbations which require systemic corticosteroids [1].

Periodontitis

Periodontitis is a chronic multifaceted inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive damage of the tooth-supporting tissues presented clinically through the loss of attachment, bleeding, pocketing and radiographically through alveolar bone loss. If this disease is left without proper management, it may lead eventually to loss of the involved tooth/teeth [7].

Like asthma, periodontitis is a major health burden affecting all populations with wide global distribution. This condition is highly prevalent and negatively affects function and aesthetics leading to reduced quality of life. Periodontitis is responsible for a high proportion of full and partial edentulism and masticatory disability [8].

The global burden of periodontitis increased from 1990 to 2019, in 2019 there were 1.1 billion cases of severe periodontitis world-wide. Its prevalence is higher among less developed countries/regions [9].

Now it is considered that severe periodontitis is the sixth most common disease globally, with an overall prevalence of 11.2% and around 743 million people having this condition, the prevalence of periodontitis rises with age, and the incidence increases steeply in adults aged 30–40 years. Such burden of periodontitis will continue to rise with the growing age of the population also due to increased teeth retention globally [8].

Globally, overall cost of periodontitis burden is estimated to be 54 billion US dollars in direct costs and further 25 billion dollars indirectly, these high costs came also from the significant contribution of periodontitis to teeth loss and the need to replace them [10].

Gingivitis is the first stage of the response of the periodontium towards local factors present in the oral cavity; this is a reversible type of response without the loss of any bony or periodontal support [11]. That means the inflammatory process during gingivitis is confined in the gingival tissues (epithelium and connective tissue) that do not extend to the periodontal tissue like periodontal ligament and alveolar bone, however; gingivitis is an important prerequisite for the development of periodontitis [11].

According to many studies periodontitis begins and continues to evolve through a complex set of interactions between the causative plaque biofilm and the host immune response. Although the biofilm is necessary for the commencement of the disease, but immune system (primarily through the inflammatory pathway) is the one which causes most of the damage [10].

Recent advancements in microbiome and molecular studies led to the notion that periodontitis is not an infection in the true meaning but rather is linked with bacterial dysbiosis and periodontitis is not caused by a single bacterium or few periodontal pathogens but is associated with changes in the quantity or effect of individual bacterium within the plaque community relative to their quantity or effect in health [11].

In reviewing the link between periodontitis and certain systemic diseases we can find that periodontal diseases and some systemic disorders share similar genetic and/or environmental etiological factors and, therefore, affected individuals may show manifestations of both diseases. Hence, loss of periodontal tissue is a common manifestation of certain systemic disorders, which could have important diagnostic value and therapeutic implications [12].

A considerable number of studies are present which support the claim that there is an association with several systemic diseases, with various levels of evidence, an association between periodontal disease and cardiovascular disease, diabetes mellitus, rheumatoid arthritis, adverse pregnancy outcomes. and respiratory diseases have been established. However, the true nature of this association, if it is causal, still remains not conclusive [13,14].

Causation is a different notion, and any given disease can be caused by more than one mechanism, and every causal mechanism involves the joint action of a multitude of component causes. We may have to accept that while we may conclude that periodontal disease is connected or associated with a certain disease this will not lead to a complete explanation or understanding of that disease; just as identifying the risk factors for falling does not provide us with a theory of gravity.

The periodontitis-systemic conditions connection could be illustrated by randomized controlled trials (RCT) on periodontal interventions to estimate the effects that periodontal treatment could have on decreasing the incidence, progression, and complications of systemic conditions which may be informative as has been shown in the past, these interventions may be beneficial even in the absence of a full recognition of the mechanisms leading to a particular disease or condition [15].

During periodontitis, locally produced pro-inflammatory cytokines such as IL-1, IL-6, tumor necrosis factor alpha (TNF-α), and prostaglandin E2 (PGE2), may translate into the systemic circulation and subsequently have a considerable change on distant organs and establish or increase an inflammatory state. In fact, compared to subjects with a healthy periodontium, patients with periodontitis have higher values of circulating white blood cells (WBC) and/or of systemic inflammatory parameters such as C-reactive protein (CRP), a protein produced by the liver in a response to an external insult. These observations have generated the hypothesis that the local inflammation caused by periodontitis may extend to a systemic level impacting the subject's inflammatory load and vice versa [16].

Usually, periodontitis causes increased local cytokines production (especially the pro-inflammatory one) where they could be transported to the systemic circulation and perpetuate an existing altered inflammatory condition, this leads to the introduction of the concept "low-grade inflammation" (LGI) [17].

LGI is characterized by a low-grade chronic systemic production of inflammatory mediators. To date, LGI is known as a risk factor for a number of chronic conditions including cardiovascular, cerebrovascular and neurodegenerative diseases, and cancer, and according to this concept, periodontitis might contribute, at least in part, to the development and progression of chronic systemic diseases by consistently inducing a state of LGI, a quiet risk factor for many of these diseases [17].

Golub *et al.* tried to answer the question on how some systemic disease and periodontitis are interconnected by suggesting the "two-hit" model. In this model, the initial "hit" involves the increased existence of anaerobic bacteria and their antigens in the periodontal microenvironment. This initial hit triggers the damaging events of periodontitis, such as increased production of bone-resorptive cytokines (IL-6, IL-1, TNF-α) and tissue-destructive matrix metalloproteinases (MMPs). The second "hit" involves a systemic condition, that causes raised levels of serological markers of systemic inflammation which may further induce immune cells in the periodontium and augment the production of MMPs, which aggravate the destruction of non-mineralized and mineralized connective tissues in the periodontium [18].

The ability of oral microbiota to invade and flourish in non-oral sites could unbalance homeostatic tissue responses in their new residence and potentially contribute to disease. Since oral pathogens flourish within anaerobic periodontal pockets, the virulence factors which facilitate successful oral colonization may also render them capable of thriving at other sites. Indeed, prominent oral pathogenic bacteria including *F. nucleatum*, *P. gingivalis*, and *A. actinomycetemcomitans* have been detected in a multitude of extra-oral tissue sites, including the lung, heart, gut, placenta, and inflamed joints [19].

Several renowned oral microorganisms have been implicated in systemic diseases. The periodontal pathogen *P. gingivalis* had been connected to cardiovascular diseases, respiratory disease, early fetal loss, and rheumatoid arthritis, where local and systemic inflammation is suggested to be the

driving factor. *F. nucleatum*, in addition to its role in bridging plaque biofilms and in oral diseases, has been implicated in a range of systemic conditions, including gastrointestinal abscesses, acute appendicitis, and pancreatic cancer [20].

A. actinomycetemcomitans can disseminate to neighboring cells, spreading via membrane-attached vacuoles endocytosed by adjacent host cells. Indeed, even a site like the brain, with a restrictive blood-brain barrier, is not saved from invasion by oral bacteria; oral *Treponema* spirochetes have been found in human brains of patients having Alzheimer disease and in branches of the trigeminal nerves, indicating a possible route of access to the demented brain. In addition to an outstanding invasion potential, periodontal bacteria possess a comprehensive array of virulence factors which facilitate colonization at extra-oral sites; fimbriae, adhesion factors, and capsules are just some components of an arsenal that provide oral bacteria with the power to survive outside the periodontium [19].

It has been considered that there are several pathways by which oral bacterial infectious diseases affect systemic diseases. Bacteremia as direct pathway, oral bacteria residing in the oral cavity invade blood vessels in dental pulp and periodontal tissues and then reach not only the heart but also the large blood vessels and various organs to cause systemic diseases. Another direct pathway involving aspiration, which often occurs in elderly patients, involves oral microorganisms reaching the respiratory system via pharynx and airway route, and causing respiratory illness [20].

The last suggested pathway is through the oral-GIT axis, where displaced portions of oral biofilms make their way through the digestive system to the gut, protected in the biofilm from the acidic stomach environment [21].

Much research had been conducted focusing on the relationship between periodontitis and diabetes, both of them are quite prevalent, chronic, non-communicable diseases with extreme public health challenges [22]. Periodontitis had been depicted as the 'sixth complication' of diabetes, and there is clear evidence of a bidirectional link between diabetes and periodontitis, with each having negative impacts on the other [23].

The risk of periodontitis is increased 2-3 times in people with diabetes compared to persons without diabetes, and the level of glycemic control is the key in determining the risk, similar to the other complications of diabetes, the risk for periodontitis increases with poorer glycemic control [24].

When considering the relationship between the two diseases in the other direction, i.e. the impact of periodontitis on diabetes, the proposed mechanism linking the two conditions is that periodontal microbiota and their products, together with pro-inflammatory cytokines, enter the circulation and contribute to upregulated systemic inflammation, this leads to impaired insulin signaling and insulin resistance, thus exacerbation of diabetes [24].

In a recent systematic review and meta-analysis by Kim *et al.*, exploring the association between periodontitis and obesity and found a positive association between them regardless of age and country [25].

The Possible Connection Mechanisms between Periodontitis and Asthma

The First attempts to study the relationship between asthma and periodontal diseases started in the 1970s and continued till nowadays, some of the mechanisms researched in the literature tried to interpret the relationship were the aspiration of the periodontal pathogens and the hematogenous spread of pro-inflammatory mediators produced locally in the periodontal pocket [26].

Till now no direct causality had been proven between periodontal diseases and asthma, but a strong body of evidence supports an association between them. People with periodontal infection probably are five times more likely to have bronchial inflammation compared to healthy controls [27].

Many researchers claim that asthmatic people are more prone to oral infections due to biofilm accumulation and saliva reduction compared to healthy individuals. In a systematic review and meta-analysis by Ferreira *et al.* in 2019, evaluating eleven studies, ten of which found an association between asthma and periodontal disease and using the meta-analysis in the same review asthmatics demonstrated more periodontal damage to dental supporting tissues, compared to patients without asthma [28].

In a recent study by Ibraheem *et al.*, 40 patients were enrolled and out of which 20 were asthmatic and 20 were non-asthmatic, showed that greater periodontal destruction was found among asthmatics patients. Greater tooth loss, bone loss percentage, and a significantly greater attachment loss were found in the asthmatics [29].

In a nation-wide survey in Korea comprising almost 6,000 participants, asthmatic patients were 5 times more likely to have periodontitis (adjusted odds ratio [OR]), and patients taking scheduled (not as-needed) anti-asthmatic medications are less likely to be diagnosed with periodontitis [30].

In another cross-sectional study in Korea, a total of 227,977 participants from the Korean Community Health Survey 2015 were recruited. Those participants were questioned about their subjective oral health and divided into very good,

good, normal, poor, very poor. Subjective periodontal status (mobility, calculus, bleeding, swelling), tooth brushing habits and scaling within the past 12 months, previous physician diagnosis of allergic rhinitis and asthma were also surveyed [31].

After adjusting covariates, a higher prevalence of asthma (3.6%) was reported in the poor oral health group than in the good (1.8%) and normal (2.1%) groups (P<0.001). Poor oral health status was significantly related to asthma, with an adjusted OR of 1.19 (95% CI =1.07-1.33, P=0.002) [31].

In a recent study, Brasil-Oliveira *et al.*, compared the oral health-related quality of life in patients with severe, mild, and no asthma and found that both periodontitis and reduced salivary flow rate were more significant in the severe than in the mild-no asthma patients [32].

In 2010 Stensson *et al.*, published a research that investigated the caries profile and gingival condition in 12- to 16-year-old with long-term asthma (n=20) and a matched healthy control group (n=20), and found that those adolescence with long term asthma had more caries risk, more gingival bleeding, and reduced salivary flow in comparison to the healthy controls [33].

Stensson *et al.* conducted another study concerned with oral health status in young adults (18–24) with controlled asthma, it was found that the asthmatics had more initial carious lesions, more gingival inflammation, and decreased stimulated saliva. It was also noticed that 65% of the asthmatic cases were mouth breathers, whereas in the control group they were 10% [34].

The lung has its own distinct microbiome, and evidence suggests that this microbiome arises from the oral microecosystem [35].

In a small study of nine subjects with mild to moderate chronic obstructive pulmonary disease (COPD), it was found that 21% of lung microbiota originated from the oral microbiota [36].

Many oral microbes associated with periodontal diseases like periodontitis and gingivitis are found in relatively high counts in the sputum specimens of patients with respiratory infections, suggesting a possible connection pathway between these oral pathogens and some respiratory diseases. On the other hand, oral microecosystem could act as a reservoir for respiratory pathogens as some of these have been detected in the oral niches like the tongue, saliva, periodontal pockets and dental plaque, this colonization of these oral niches may provide a foundation for subsequent infection and invasion of these respiratory pathogens of the respiratory tract [37].

In 2014, Gomes-Filho *et al.* published a paper on the association between periodontitis and asthma, in this study the included individuals were diagnosed with severe asthma, the unadjusted odds ratio was 4.3, and after adjusting possible confounders like education level, age, mouth breathing, and smoking, the likelihood of adjustments increased to about 5 times more (patients with periodontitis more likely to have severe asthma) [38].

In 2017, the same group did another case-control study on the association between periodontitis and severe asthma patients adequately controlled by the appropriate therapy to compare the results with their previous research which was performed on severe asthma patients without professional management, the authors found that periodontitis was present in the asthma group three times more than that present in the control group and this strong association remained even after adjusting the possible confounders shared between the two entities [39].

One of the proposed mechanisms for this association was that biologically active molecules produced from the host cells in response to the periodontal pathogens like tumor necrosis factor-α, interferons, and matrix metalloproteases, these molecules had been accused of inflicting bronchial remodeling leading to asthma [39].

Lopes *et al.* found a strong significant association between asthma and periodontitis with an odds ratio of 4.64 (unadjusted) among the individuals with severe asthma, 36.4% were diagnosed with periodontitis, while only 11% in the control group were diagnosed with periodontitis and this association remained significant even after considering the possible confounders like age, family income, hypertension, current smoking habits, body mass index, and mouth breathing, which were included in the adjusted model to evaluate periodontitis and severe asthma and the odds ratio was 4.00 confirming the association. In the same study the authors also evaluated the levels of important periodontal pathogens and discovered *Prevotella intermedia* had greater levels in severe asthma patients when compared to the control group with an odds ratio of 2.64 [40].

In Jordan, Khassawneh *et al.* performed research on the association between asthma and periodontitis, and they also investigated the effects of anti-asthma medications on the proposed relationship. They found that periodontitis was more prevalent in the asthma group than control group (40% and 20% respectively), asthmatic patients did have more severe cases with higher extent of periodontal lesion than healthy controls.

Regarding anti-asthmatic medications, periodontitis was more predominant in asthmatic patients receiving oral corticosteroid than inhaled corticosteroid (56% and 24% respectively) [41].

One of the most commonly used medications to manage asthmatic patient is β2 adrenoceptor agonists which promote and enhance bronchial relaxation, these receptors are also present in the salivary secretory system, and they affect saliva composition (change in the salivary proteins) as well, using β2 adrenoceptor agonists may lead to impairment of salivary secretion [42].

Increased gingival inflammation and more calculus deposition were evident among asthmatic children taking anti-asthmatic medication (inhalers and oral tablets) when compared to healthy controls [42].

Corticosteroids (mainly the inhaled ones) raise the likelihood of having periodontal diseases. Corticosteroids have immunosuppressive effects that influence the periodontal tissue response against the aggression of bacterial pathogens [43].

Inhaled corticosteroids may decrease bone mineral density and may include mandible, moderate to high doses of these drugs can increase the likelihood of bone fractures especially when using them for a long term and for that inhaled corticosteroids may have a role in periodontal disease initiation and progression [44].

Considering inhaled steroids is very effective treatment and very commonly prescribed for asthmatics. Moosavi conducted research to find the effect of inhaled steroids used by asthmatic children on salivary beta-defensin 2 which has anti-microbial activity and an important role in innate immune response. In this study it was found that the salivary protein had lower concentration after treatment with inhaled steroid compared with its concentration before commencing the treatment [45].

Although in the previous paragraphs we mentioned many studies which found a positive association between asthma and periodontitis, on the opposite direction many studies did find an inverse type of relationship, and some studies did not find any sort of association which refer to the diverging finding in the literature regarding asthma and periodontitis, these conflicting results may be attributed to the shared risk factors like smoking, ethnicity and obesity [46].

Also in the different studies searched for the possible association, there were no standardizations in defining periodontal diseases and asthma leading to inconsistent results [46].

To have some examples on studies that did find an inverse relationship between asthma and periodontitis, Rivera *et al.* performed research on the relationship between periodontal disease and asthma in obese adults and they found that patients with severe periodontitis were less likely (odds ratio for having asthma 0.44) in compassion to patients diagnosed with none/mild asthma. Also, in the same research an inverse relation was found between periodontitis (especially severe cases) and using asthma medication, compared to asthma prevalence/periodontitis model, patients with severe (and moderate periodontitis) had even lower probability for using asthma medication (odds ratio for taking asthma drugs 0.2) [46].

In nationwide research in the United States that used data from almost 10,000 adults who took part in National Health and Nutritional Examination Survey from 2009 to 2014, current asthmatic patients had lower odds of having severe periodontitis compared to healthy non-asthmatic persons [47].

In an interesting research (case-control study conducted on 892 participants with 50% asthmatic patients and 50% healthy controls) performed at the University of Michigan School of Dentistry by Saleh *et al.,* a strong inverse relationship was found between asthma and periodontitis with an odds ratio of 0.10 (90% lower probability of asthmatic patients to develop periodontitis). On studying the effect of smoking on the results in the asthmatic group, smoking increased the odds for having periodontitis especially the former smokers by over twice the odds compared to non-smoking asthmatics with current smokers almost have similar but slightly lower increase in the odds [48].

Also, asthmatic patients on adrenergic inhalers were found to be more likely to develop periodontitis (odds ratio 1.76) and have more severe periodontal lesions and more advanced grades [48].

Some of the mechanisms proposed by the authors for this alternate relationship are asthmatics may intentionally follow a healthier lifestyle with more emphasis on their oral health and more regular prophylaxis and more dentist visits. Also, there may be a shift in the microbial flora from a more periodontopathogens to a more cariogenic one, another mechanism include immunological one which is associated with asthma-related inflammation resolution that is higher levels of T helper 2 (Th2) lymphocytes in asthmatics can suppress the damaging effect of osteoclasts in the periodontal lesion [48].

In another recent study that used data for both asthma and periodontitis obtained from Genome-Wide Association Study (GWAS), this study used the Mendelian randomization (MR) analysis and consistently found asthma may be a protective factor (inverse relationship) against having periodontitis, and when performing the reverse analysis there was no evidence of causal effect of periodontitis to bring about asthma [49].

Friedrich *et al.* studied the relationship between periodontitis and respiratory allergies including hay fever, house dust mite

allergy, and asthma. Regarding hay fever, house dust mite allergy and periodontitis increasing in attachment loss show a decreasing trend. With regard to asthma and periodontitis, it was observed that there was a slight inverse relationship [50].

The same group after two years published another paper aiming to investigate the relationship between periodontitis and respiratory allergy in patients with type 1 diabetes, like the previous study with increasing in attachment loss there was decreasing risk to have respiratory allergy [51].

In a nation-wide study in the republic of Korea that tried to find the nature of relation between periodontitis and allergic rhinitis (disease condition closely related to asthma), which included 6,129 adults used the data concerning history of treatment of periodontitis as an indication of periodontitis diagnosis to find a relation with allergic rhinitis. This condition was diagnosed in 11% of those with previous periodontitis treatment and 17.5% of those without periodontitis, from this perspective there is 1.53 fold higher chance to have periodontitis in the healthy (non-allergic rhinitis group). A possible explanation for this inverse relation is the T-helper (Th1/Th2) theory that is based on the homeostasis of the activities supervised by Th1/Th2 cells, that is the upregulation of cytokines related to Th1 (usually associated with inflammatory pathways) can inhibit Th2 cytokines (usually connected with allergic diseases) and vice versa [52], this has also been shown in an animal experiment on mice where both asthma and periodontitis were induced experimentally and after evaluation the asthma group showed increased Th2 related cytokines while periodontitis group had increased Th1 cytokines profile [53].

Also, the difference in the prevalence of allergic rhinitis and periodontitis with age may support the inverse relation, that is periodontitis usually increase with aging while allergic rhinitis patient in which children make up 40% of all allergic rhinitis cases [52].

One of the possible explanations for the inverse relation between asthma and periodontitis that was introduced by some authors is the hygiene hypothesis.

This hypothesis was presented more than three decades ago by D.P. Strachan in 1989, in his study he observed that children live within large families had less occurrence of asthma and allergic diseases, in his defense he presumed that increased occurrence of infections in such large families was the reason for decline in allergy, so his hypothesis was that infection in younger ages has a protective factor against allergic diseases, the evidence and scientific explanation for this hypothesis is still lacking and cause to ongoing debate and controversy [54].

When periodontitis was induced in experimental asthmatic mice model, inflammatory cells like lymphocytes and macrophages in bronchoalveolar lavage fluid were decreased, also levels of inflammatory cytokines like IL-4 and tumor necrosis factor-α and the production of airway mucus were reduced [55].

To increase the debate and controversy, some studies did not find any association between periodontitis and asthma, in a recent systematic review and meta-analysis by Ana Molina that studied the association between respiratory diseases and periodontitis found no association between asthma and periodontitis [56].

Ho *et al.* tried to discover the association between asthma, allergic rhinitis, and oral diseases including dental caries and asthma found no association with these oral diseases and the authors attribute any previous association with oral diseases to the possible effect of allergic rhinitis as the association was present when not taking allergic rhinitis as a confounder [57].

To ascertain the relationship between asthma and periodontitis from another perspective that is the effect of periodontal treatment on asthma symptoms, in a nationwide study in Taiwan that used insurance data to have a case group of 4,771 asthmatic patients with periodontal disease who underwent periodontal treatment like scaling, gingival curettage, and flap procedure and control group of the same number who were asthmatics without periodontal disease, the authors found that the case group had lower incidence of hospitalizations for adverse respiratory events related to asthma and reduced rate of intensive care unit admissions, also the mortality rate was significantly lower in the case group [58].

A questionnaire survey in Japan with an aim to find the effects of dental treatment restriction that happened during the COVID-19 pandemic on the exacerbation of various systemic diseases (asthma included), found that abandoning dental treatment was an important factor in the exacerbation of each examined systemic condition (except atopic dermatitis and mental illnesses) [59].

The study by Pambudi *et al.* showed the benefit of professional periodontal treatment on ameliorating asthma-related symptoms in mild asthmatic children. They found that significant improvement in these symptoms occurred in the group who received periodontal treatment as shown by a decrease in asthma symptom score, improvement in bronchial airway hyperresponsiveness and also the blood eosinophils reduced significantly (although it is indirect reflection of airway inflammation) [60].

In a low number (10 participants) non-blinded randomized controlled trial which aimed to evaluate the effect of 6 months scaling and root planning in children with house dust mite allergy and gingivitis, the children in the intervention group

showed significant decrease in IgE and IgG4 serum levels (which are biomarkers for allergic conditions) in comparison to the no-treatment group. Also this small pilot study showed that untreated gingivitis is associated with worsening of allergic diseases symptoms [61].

When looking for the relation between asthma and periodontitis, the effects of smoking and obesity cannot be ignored as both of them as known from a considerable evidence to be an important risk factor for asthma and periodontitis as the existence of smoking and obesity is associated with increased severity and worsening of asthma symptoms, also smoking cessation and improving body mass index had been associated with significantly improving asthma and periodontitis condition [55].

Conclusions

This review highlighted the complex and conflicting association between asthma and periodontitis, while the current evidence point to a shared immune-inflammatory pathway, bacterial link, probable effect of anti-asthmatic medication on oral health, the precise nature of the relation remained inconsistent through different studies which points to the importance of conducting longitudinal and interventional studies to better understand the bi-directional link of these diseases.

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